A simulation platform for optimising X-ray imaging of Gold Nanoparticles

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Motivation & Purpose

Being able to visualize GNPs through X-Ray/CT imaging will provide:

- A **contrast agent** with better properties than iodine for the visualization of the circulatory system
- The radiolabeling process of the NPs – needed to follow the **targeted radiopharmaceutical root -** may be accurate but it might modify their nature and properties, whereas x-rays do not add to complexity or **modification**
- **A big number of animals is needed to test appropriate concentration of GNPs that will provide adequate contrast for each x-ray system**

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This project aims to:

- Develop a model to perform x-ray imaging studies on a simulation level
- Validate the model
- Provide a tool to optimize x-ray imaging protocols
- Provide a tool to allow reduction in the number of animals needed for an in vivo x-ray GNPs imaging study
- Confirm results in vivo

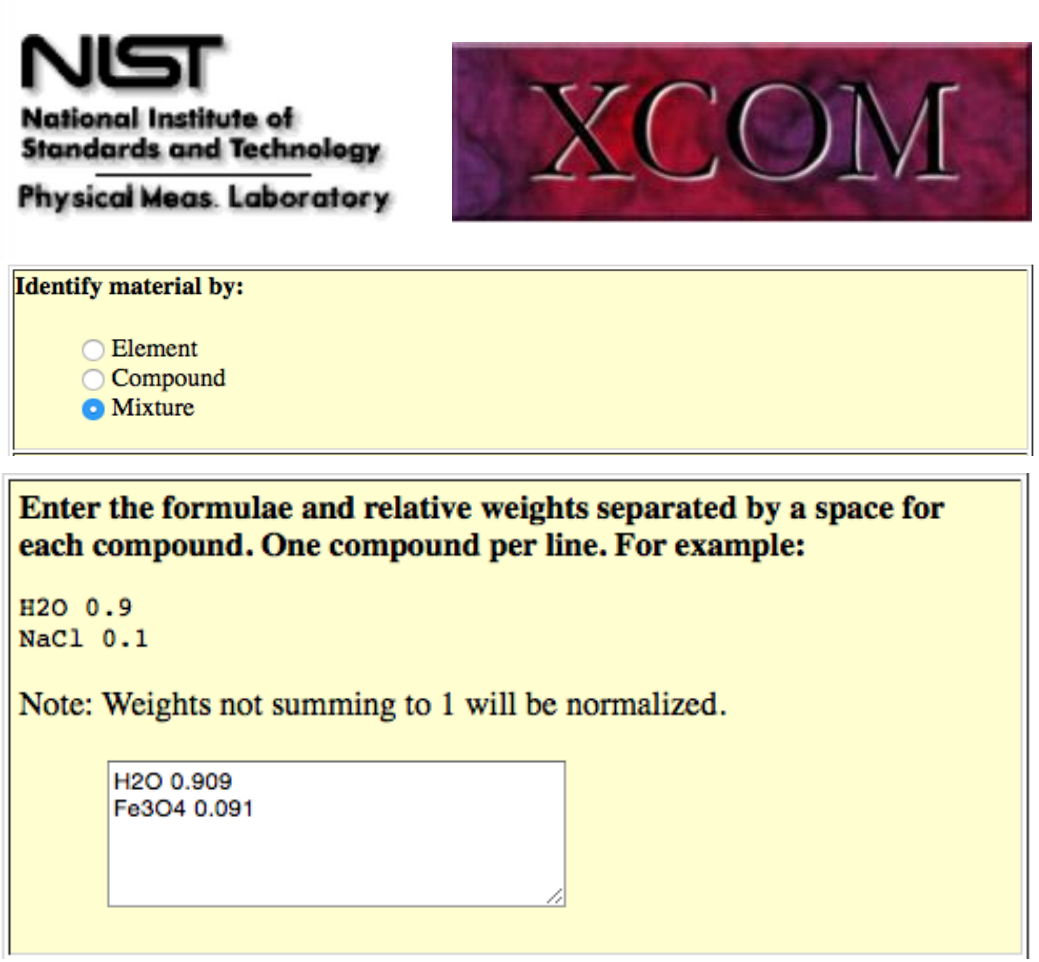
Theoretical Calculations on the attenuation of the NP solutions

- Concentrations PW (%) were used together with the solutions' densities
- Example for iron oxide calculations – 100mg/ml:

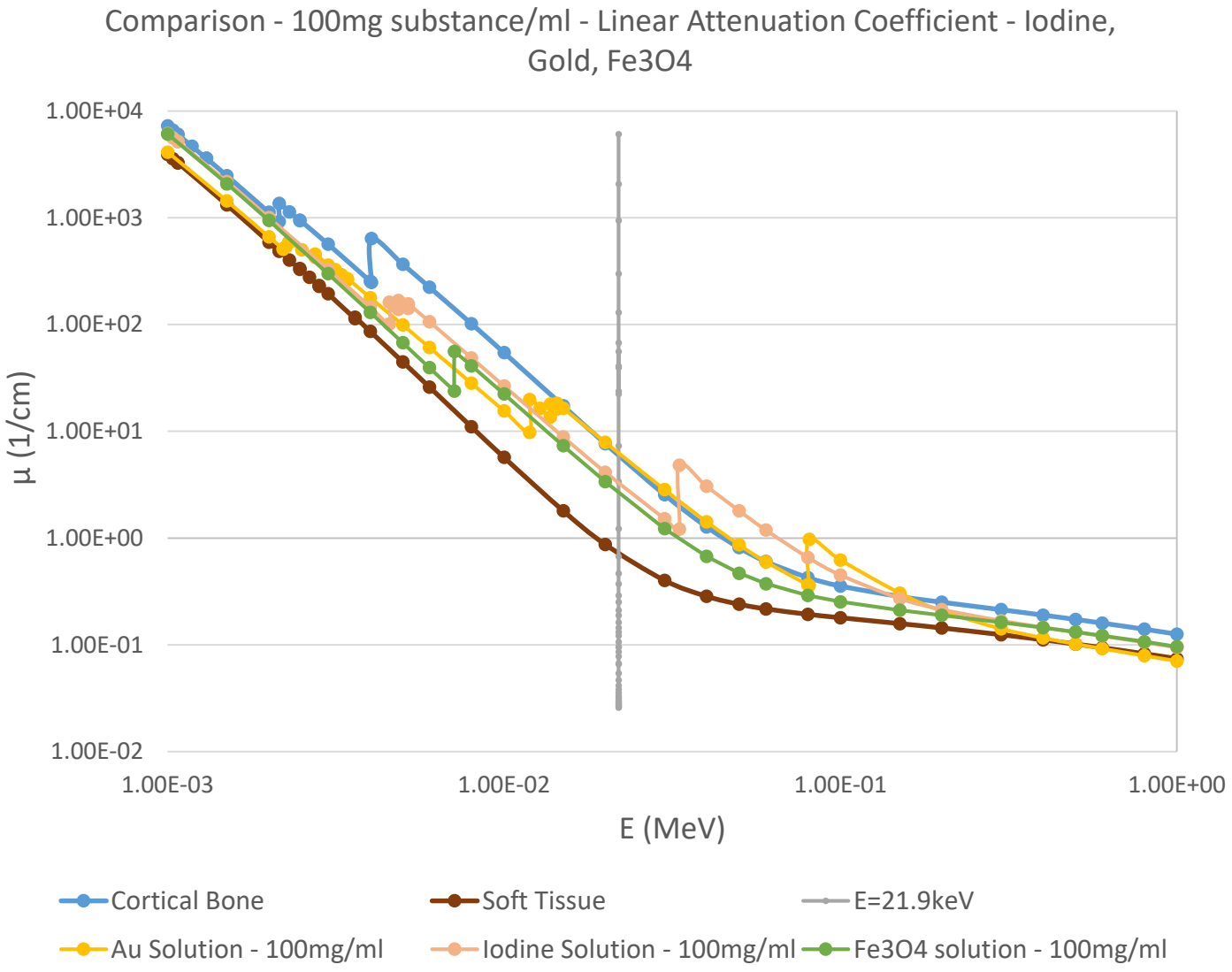
$$\rho\,(Fe_3O_4\,solution) = Conc\ PW\ (Fe_3O_4, \%) * \rho(\mathrm{Fe_3O_4}) + [1 - Conc\ PW\ (Fe_3O_4, \%)] * \rho\ (\mathrm{Water})$$

$(\mu/\rho)_{MIX}$ for all energies from NIST (e.g. for 100mg/ml)

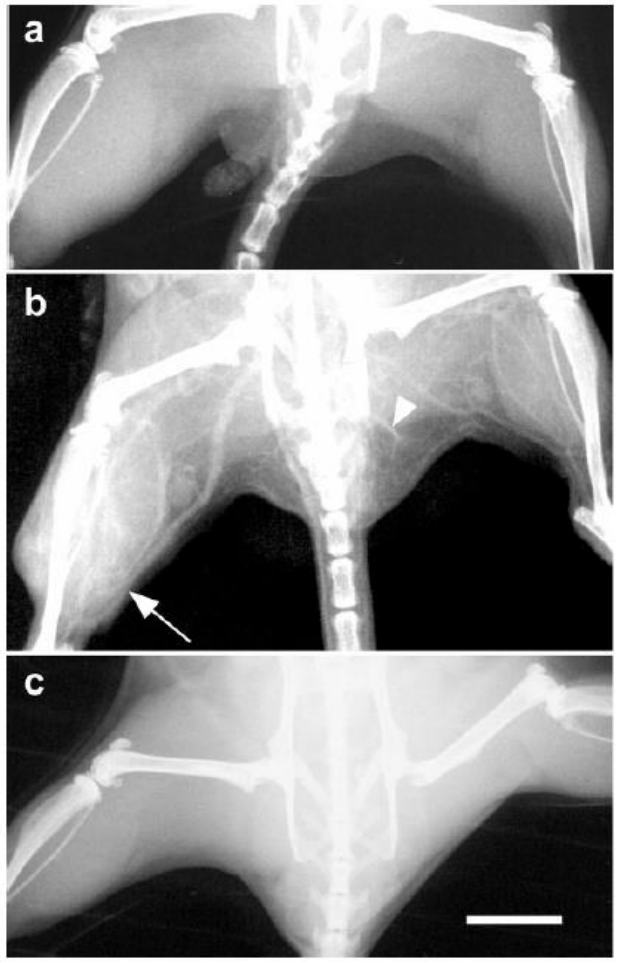
$$\mu_{MIX} = (^{\mu}/_{\rho})_{MIX} * \rho(Fe_3O_4\,solution)$$



X-Ray Attenuation – Theoretical Evaluation



An example from literature - J. Hainfeld et al (2006)



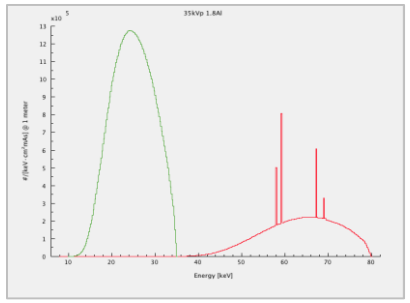
X-ray image of mouse leg **before injection** – tumour and increased vascularity

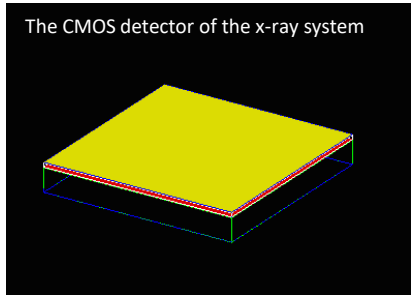
2 min after tail vein injection of **gold NPs** (AuroVist 1.9nm)

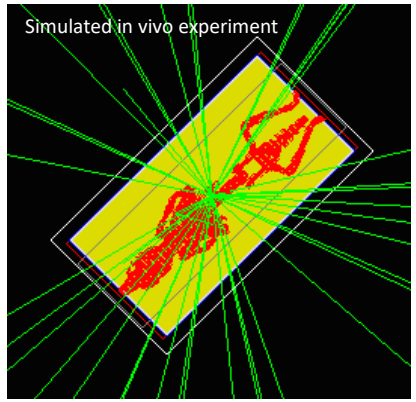
2 min after tail vein injection of **equal weight iodine** contrast agent (Omnipaque)

The platform

Simulation of the system set up







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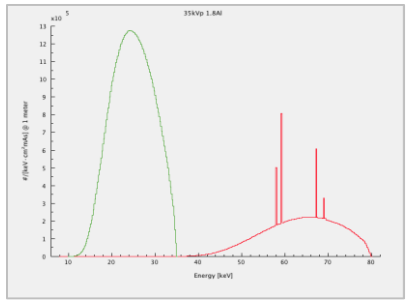
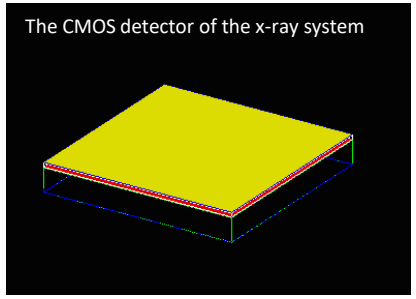
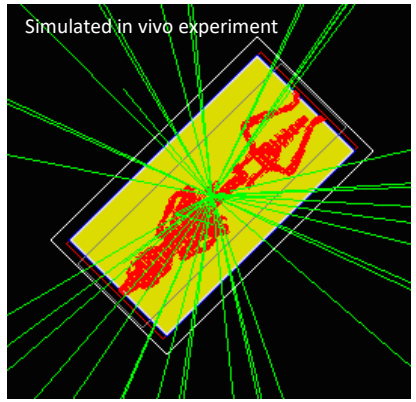
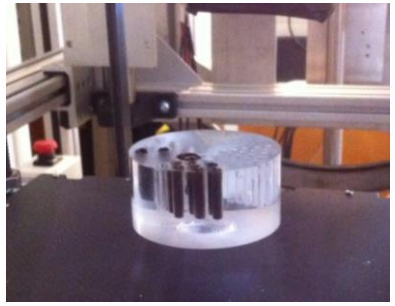
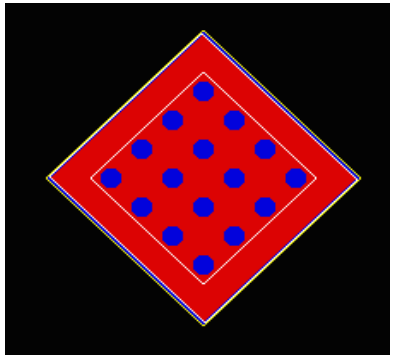


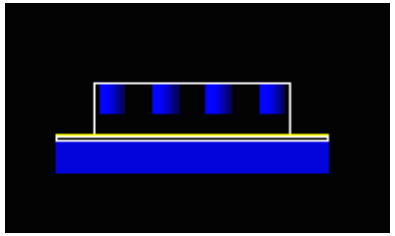




Simulation of the NPs solutions







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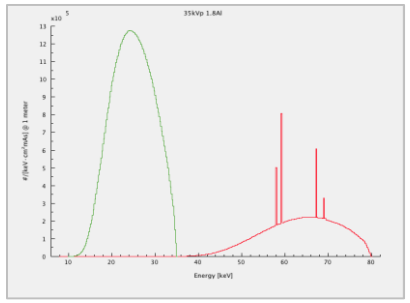
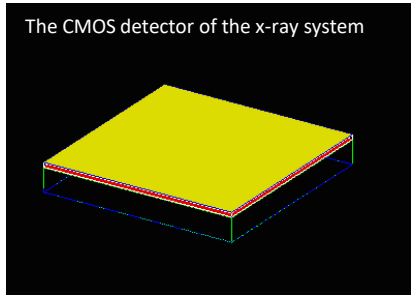
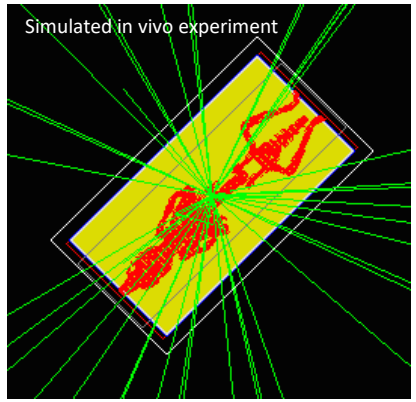


The CMOS detector of the x-ray system



Simulated in vivo experiment



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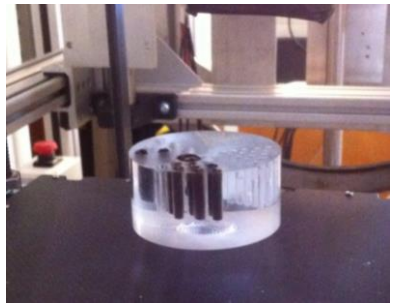
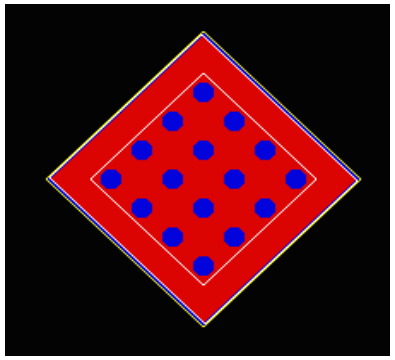
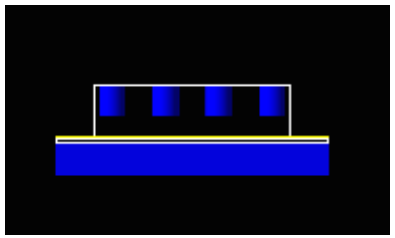
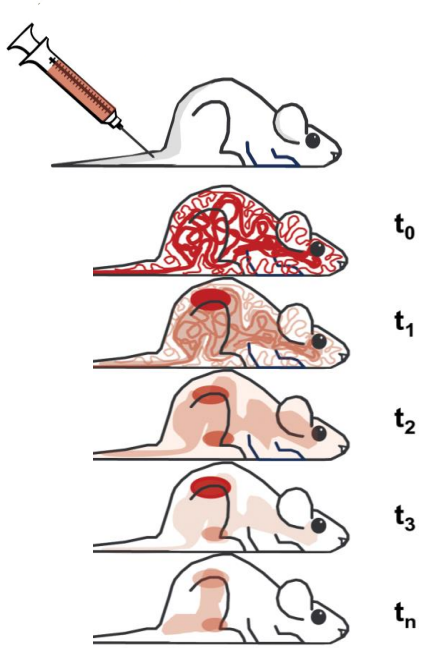
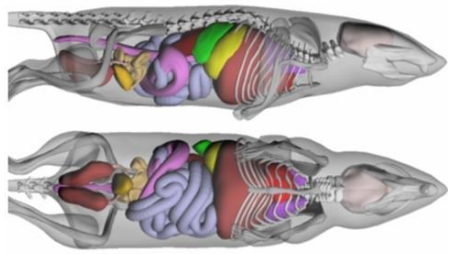






Import of the NPs bio kinetics in MOBY





http://dx.doi.org/10.1371/journal.pone.0020594

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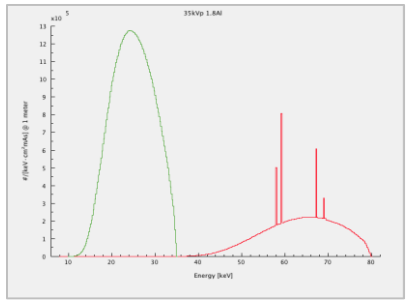
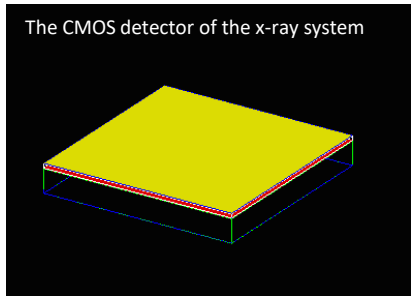
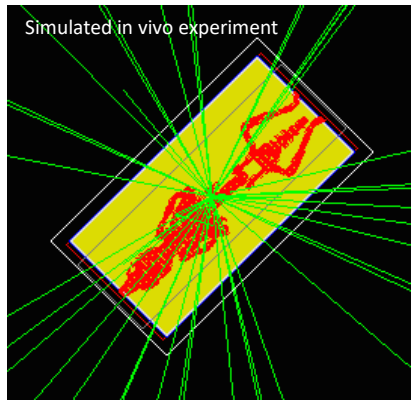
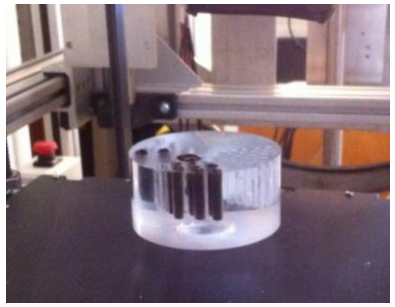
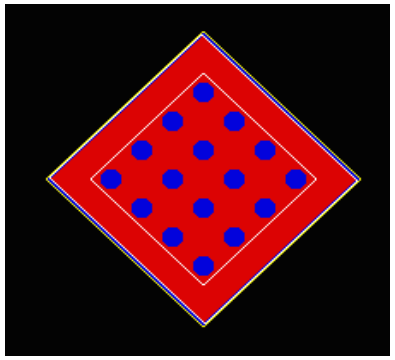


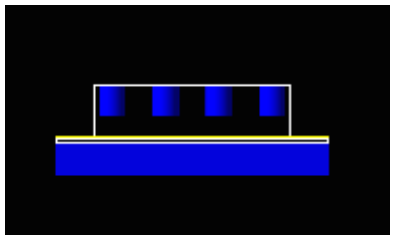




Simulation of the NPs solutions







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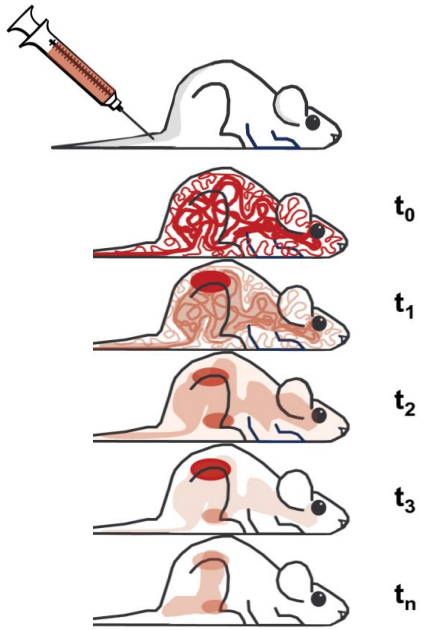
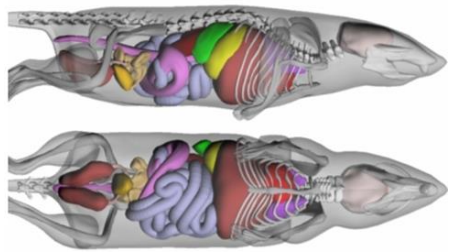
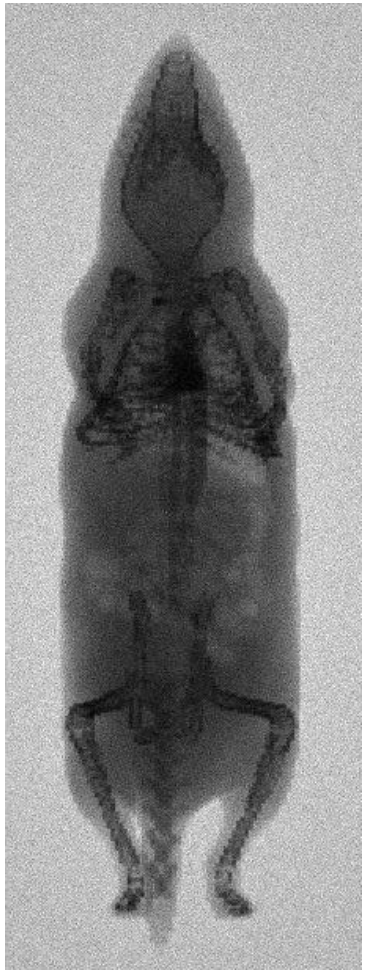




Run the simulation and export x-ray images



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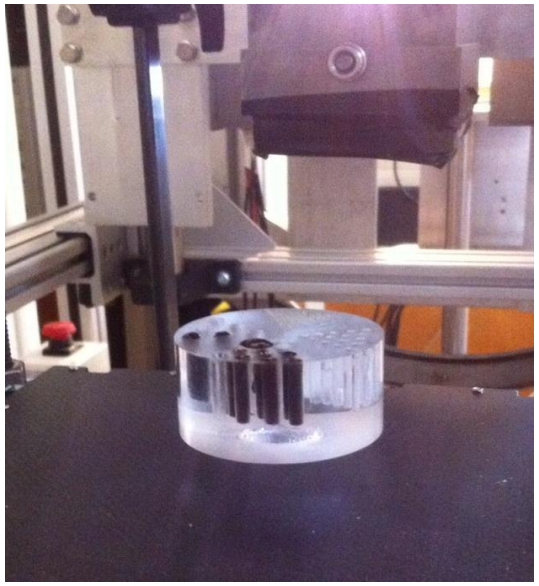
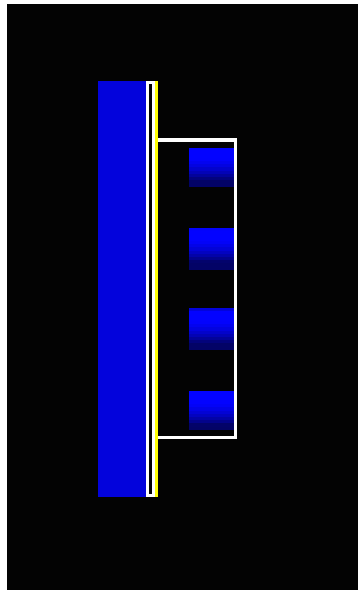
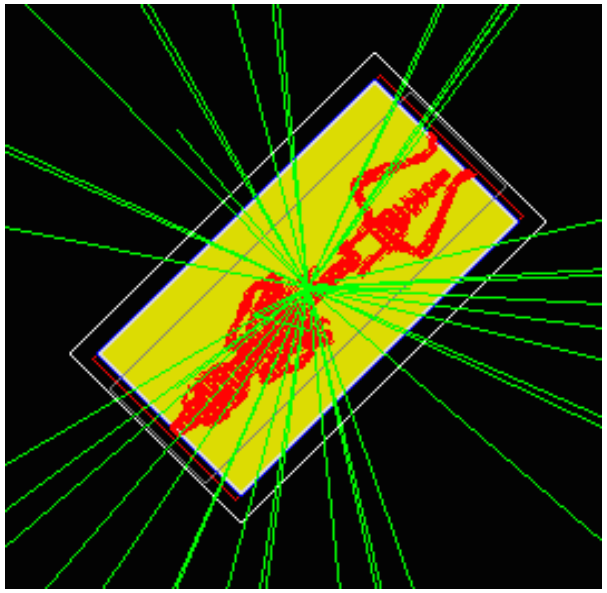
Simulation of the system set up

- Solutions of different concentrations are placed into identical holes in a PMMA phantom
- Solutions are also injected intravenously in mice
- Irradiations are performed with an x-ray beam of 35 kVp, 0.5 mA for 0.1 sec exposure time



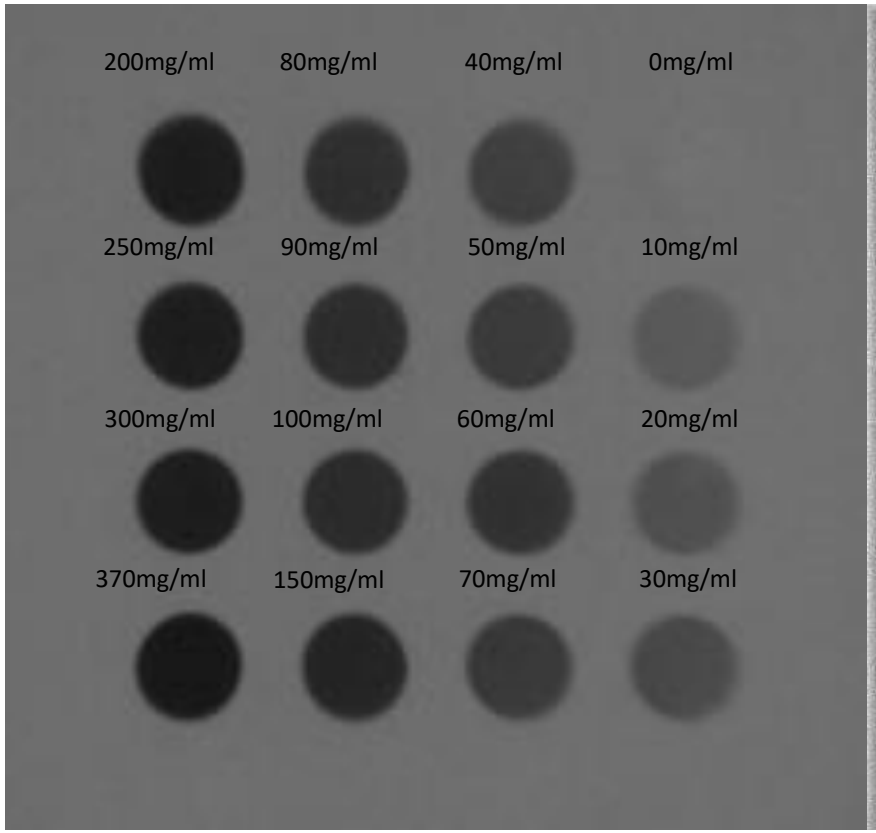
- The solutions and phantom are simulated to match the experimental conditions
- Spectrum and number of primary photons are exported through SpekCalc for any x-ray source
- MOBY computational mouse phantom



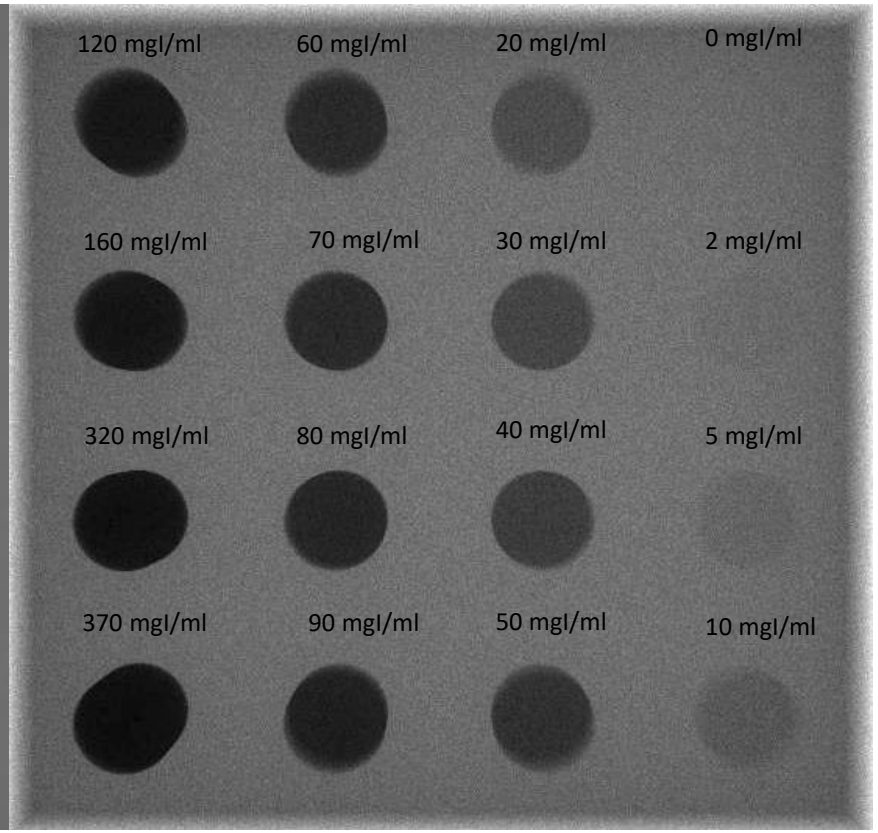


Validation of system simulation – Iodine solutions

- Validation of the beam spectrum through HVL measurements
- Validation of the whole system set up through imaging commercial iodine solutions

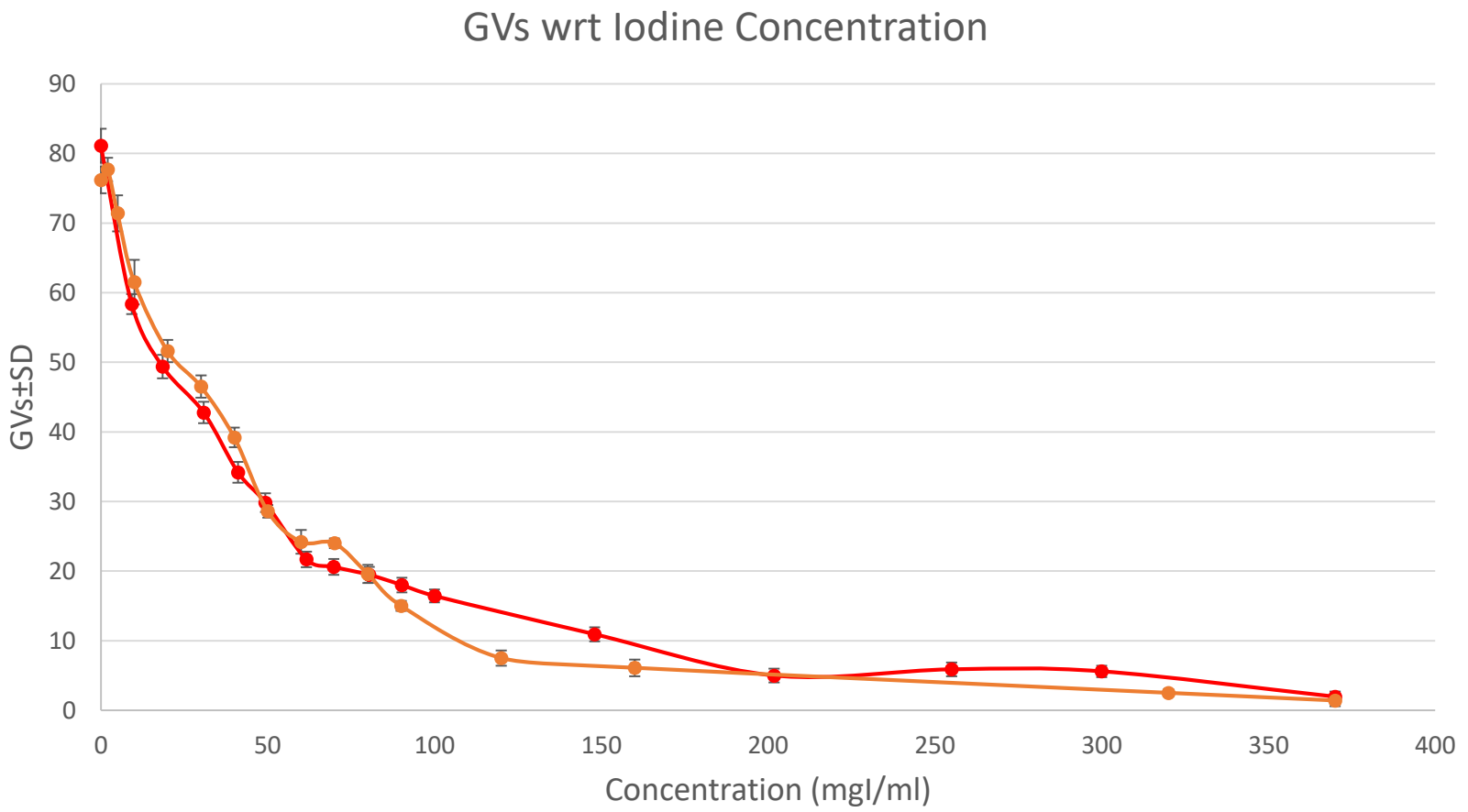


Experiment



Simulation

Validation of system simulation - Iodine Attenuation



Simulation of NPs solutions – Definition in GATE

- The simulation is based on 2 main points:

- In CT/X-ray the direct visualization of NPs is not possible, **density variations are visible** (LeBrun, 2016)
- The geometry and **size of the NPs do not affect the image** contrast (Nohyun Lee, 2013)

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❖ Definition of a compound/mixture in GATE:

1. Definition of any non-existing material (e.g. Fe_3O_4) – its density, number of elements, state, name and chemical composition

2. Name and number of all present elements/materials and their **per weight (PW%) concentration** in the mixture

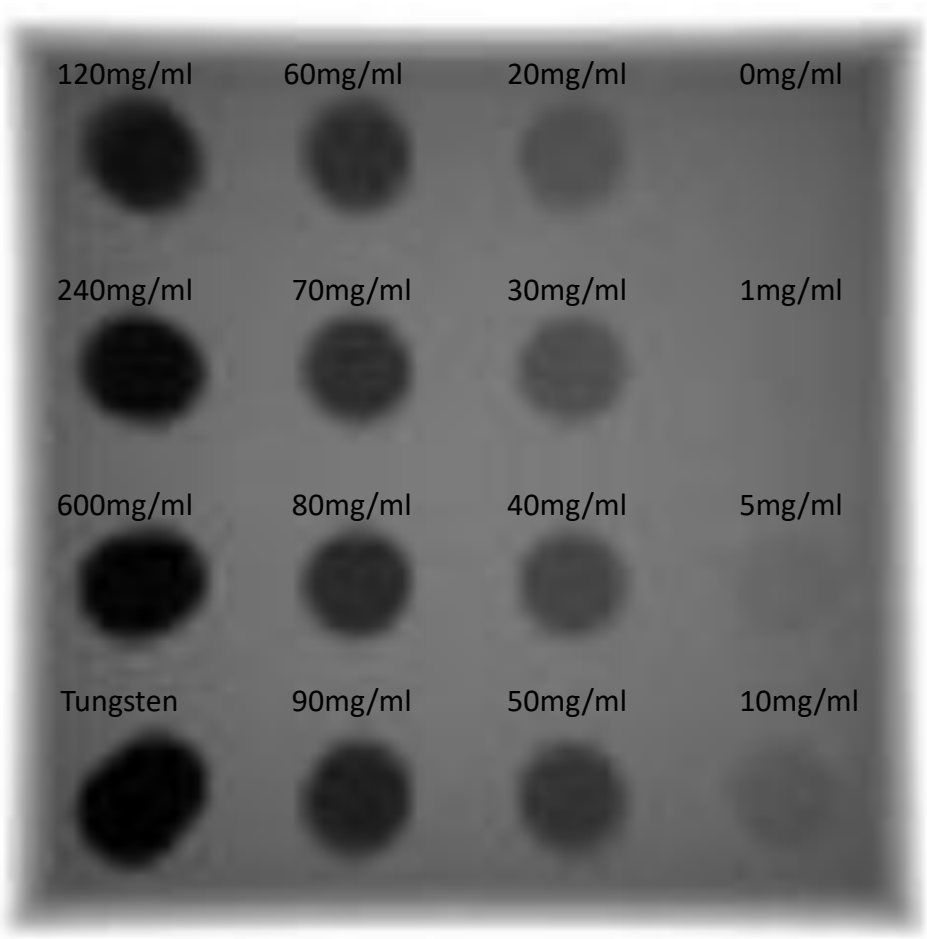
3. Name and density of compound/mixture

$$\rho\ (Fe_3O_4\ Solution) = Conc\ PW\ (Fe_3O_4, \%) * \rho(\mathrm{Fe_3O_4}) + [1 - Conc\ PW\ (Fe_3O_4, \%)] * \rho\ (\mathrm{Water})$$

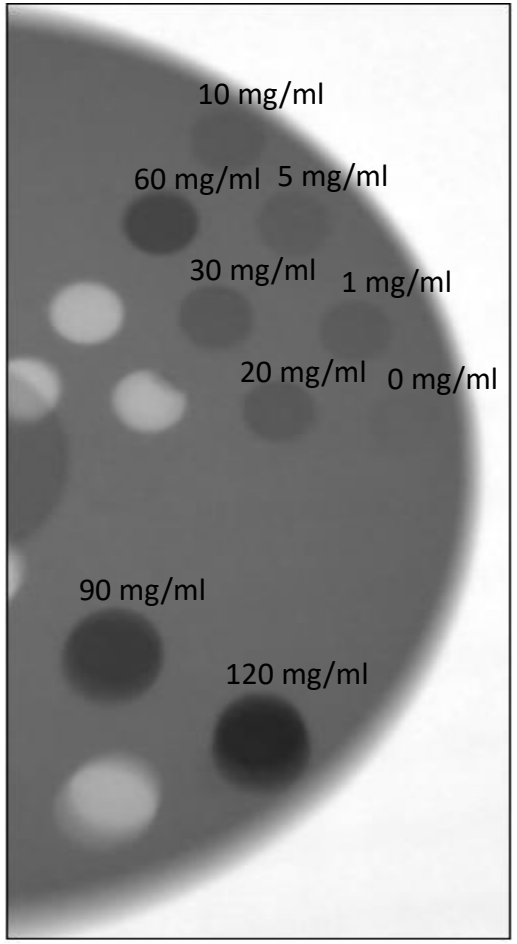
Fe_3O_4:
d=5.17 g/cm3; n=2;
state=Solid
+el: name=Iron; n=3
+el: name=Oxygen; n=4

Solution Fe_3O_4 50mg/ml:
d=1.1986 g/cm^3; n=2;
+mat: name=Water; f=0.952
+mat: name=Fe_3O_4; f=0.048

Validation of NPs Attenuation

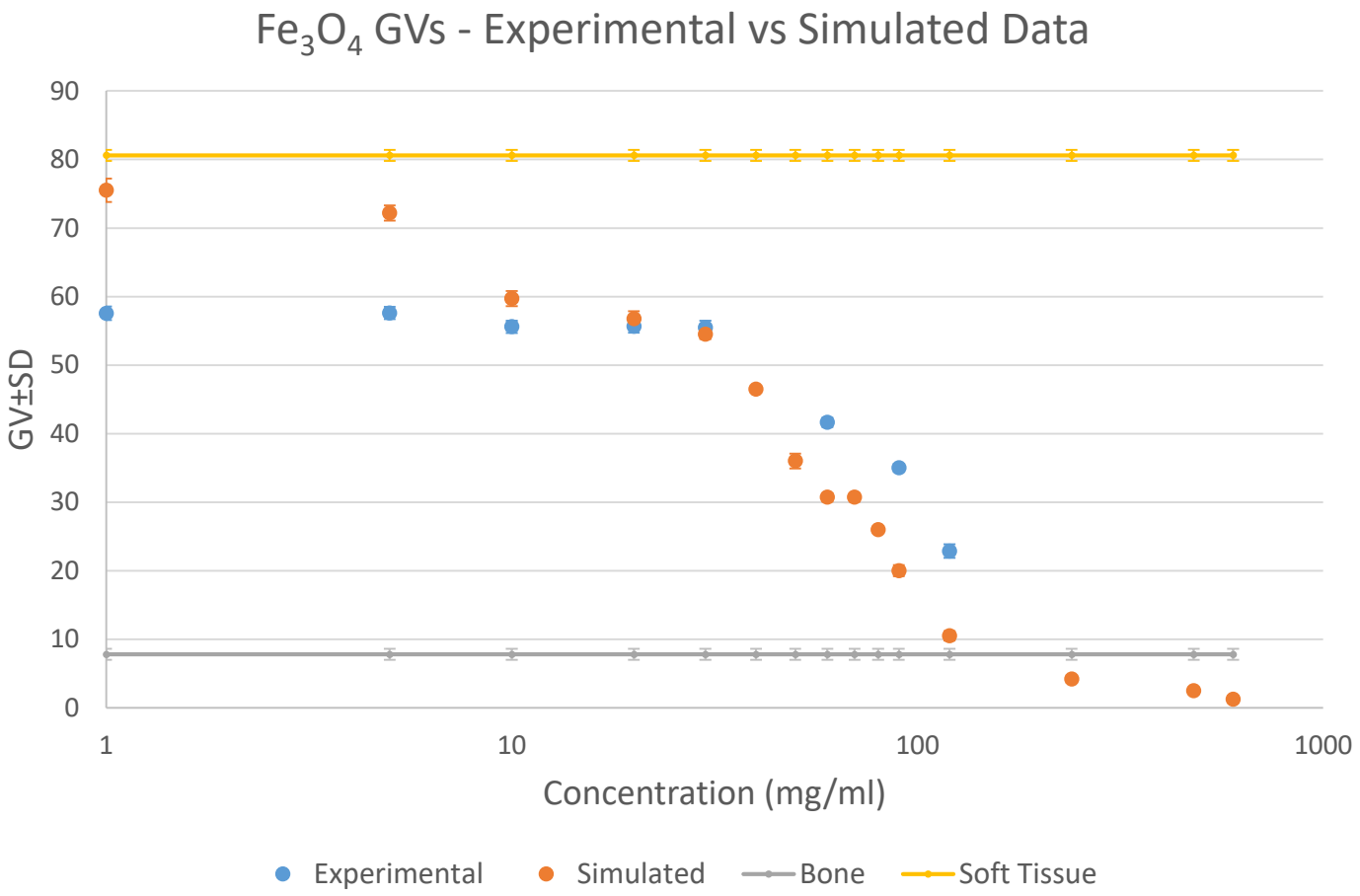


Simulation



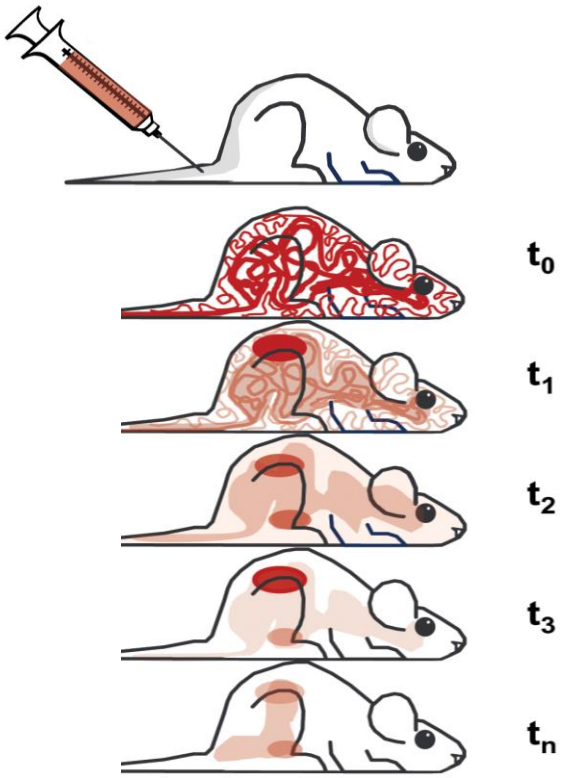
Experiment

Validation of NPs Attenuation

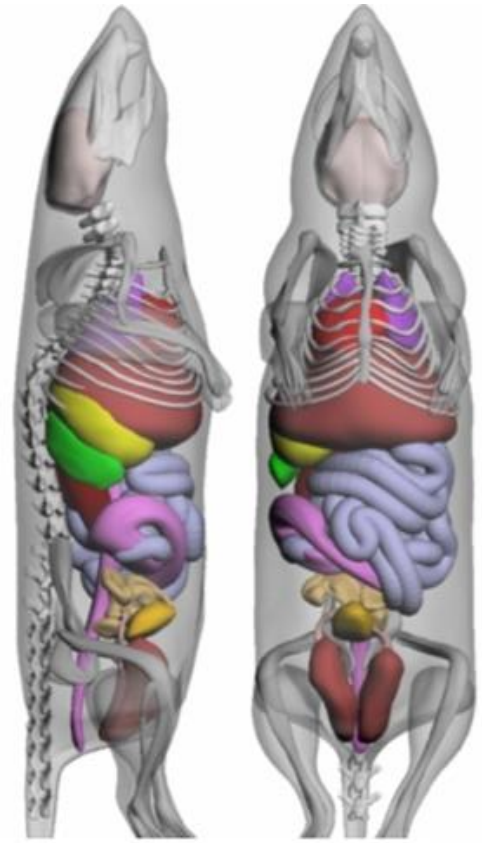


Import of GNPs bio distribution in MOBY

µg Au/g tissue or
% of given dose/tissue



Change tissue properties accordingly



Modified tissues to account for the GNPs

Liver with 20mg GNPs:

d=1.2106 g/cm^3; n=2;
+mat: name=Liver; f=0.99174
+el: name=Gold; f=0.00826

Blood with 10mg GNPs:

d=1.1749 g/cm^3; n=2;
+mat: name=Blood; f=0.9937
+el: name=Gold; f=0.0063

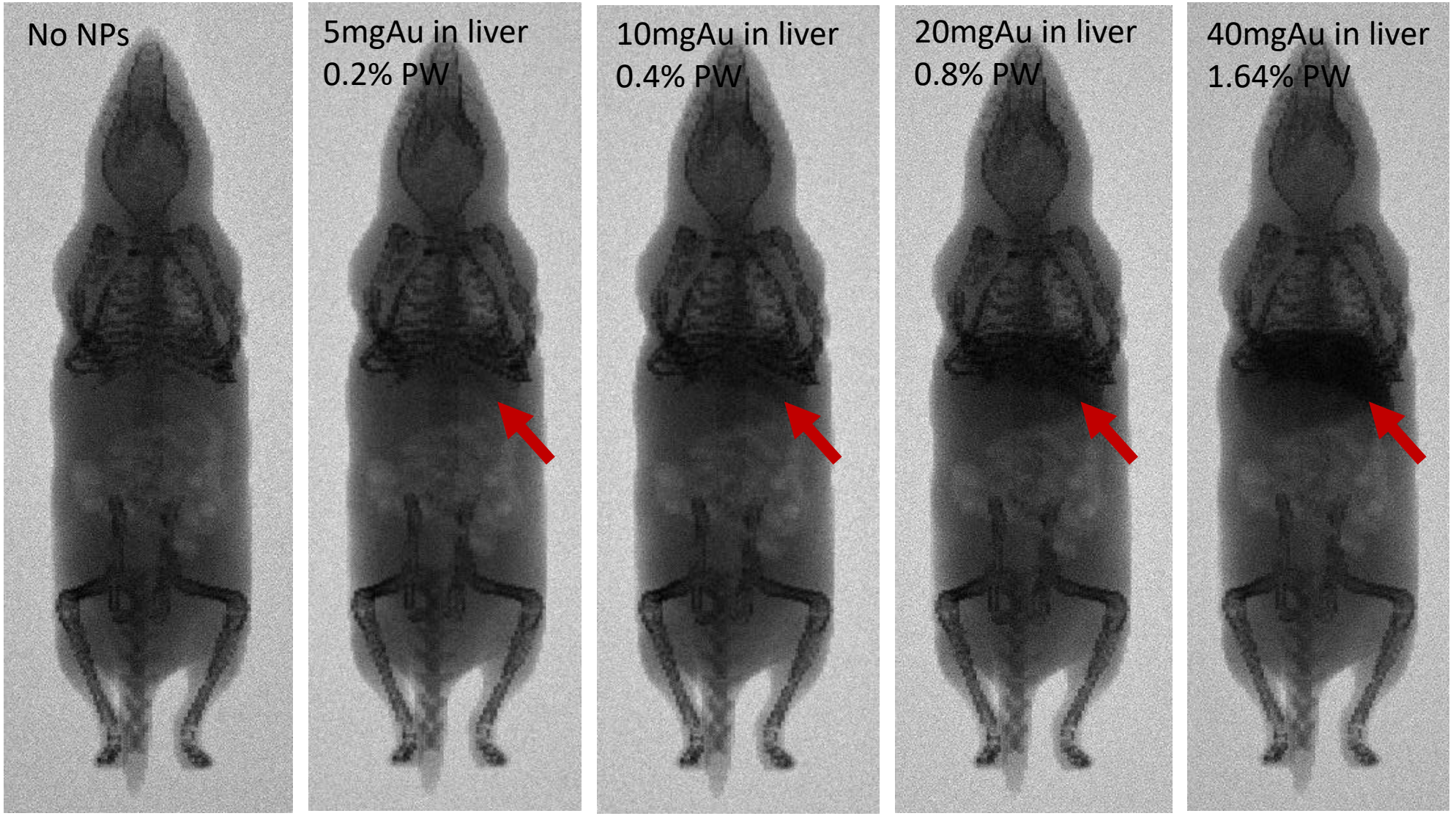
Spleen with 0.15mg GNPs:

d=1.077 g/cm^3; n=2;
+mat: name=Spleen;
f=0.99905
+el: name=Gold; f=0.00095

http://dx.doi.org/10.1371/journal.pone.0020594

Export of x-ray images

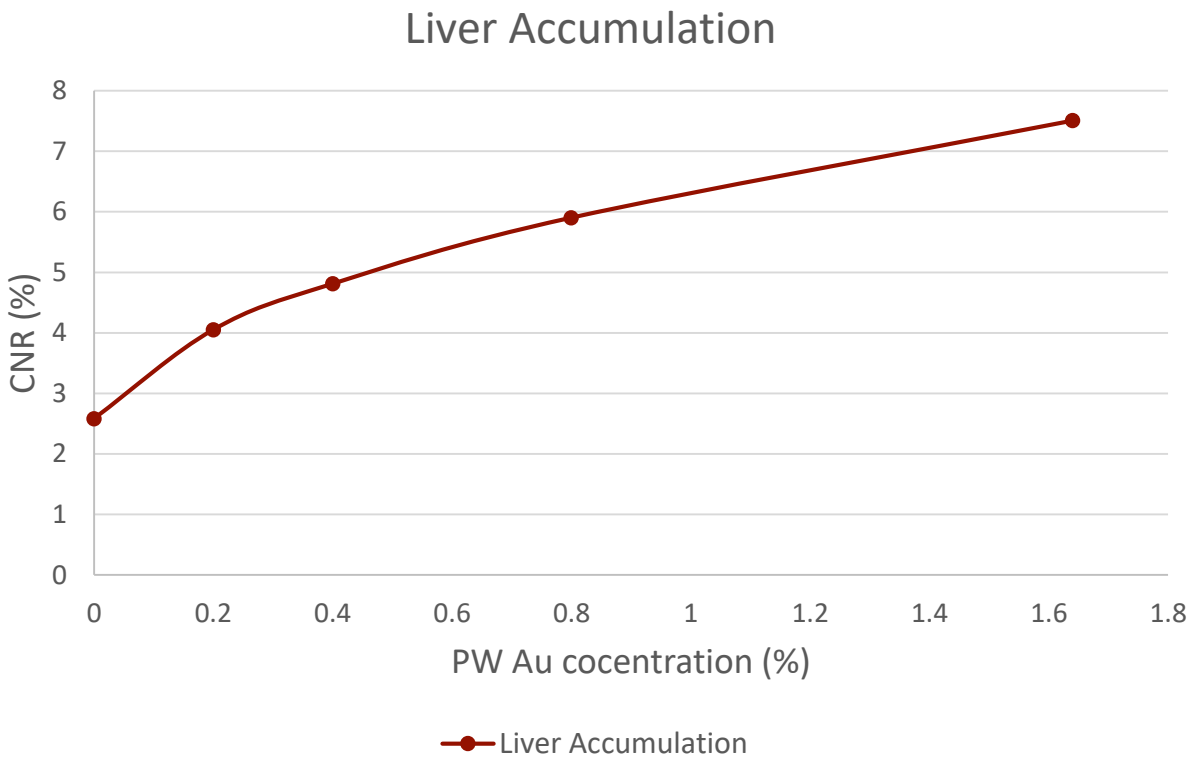
1. Full Accumulation in the liver



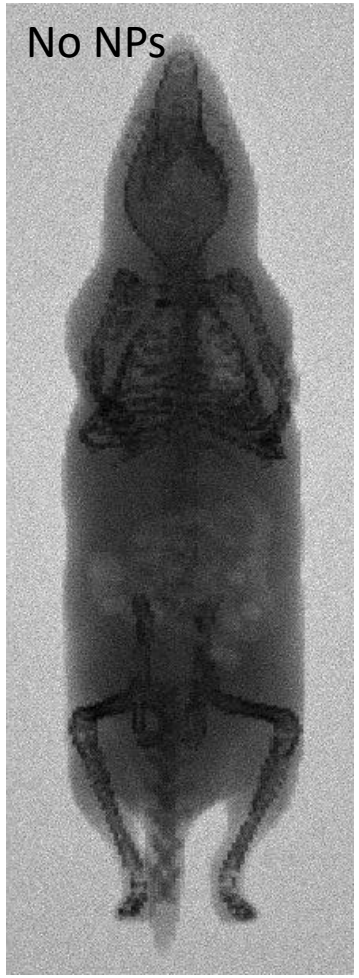
1. Full Accumulation in the liver

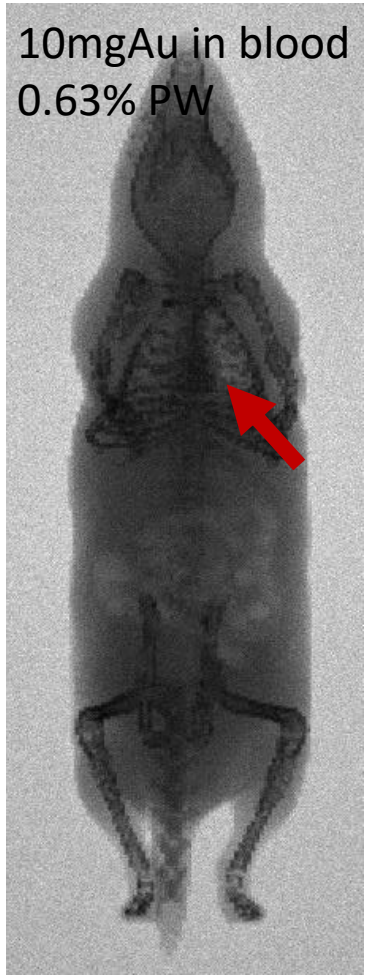
- Detectability of structures can be measured through the Contrast to Noise Ratio of the structure

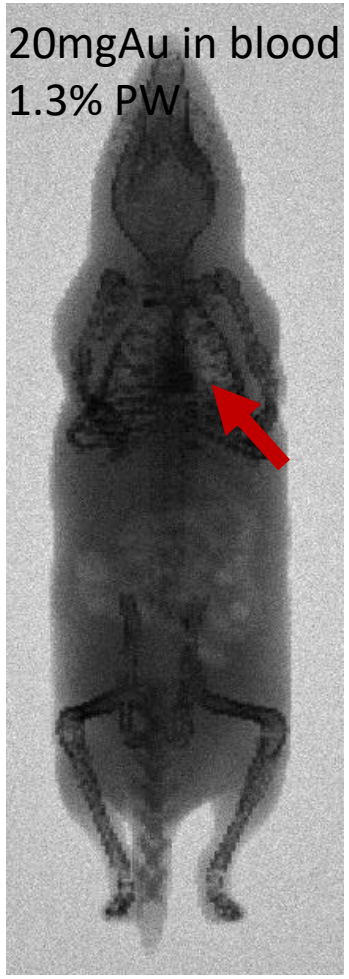
$$CNR = \frac{GVstr - GVbkg}{SDbkg}$$

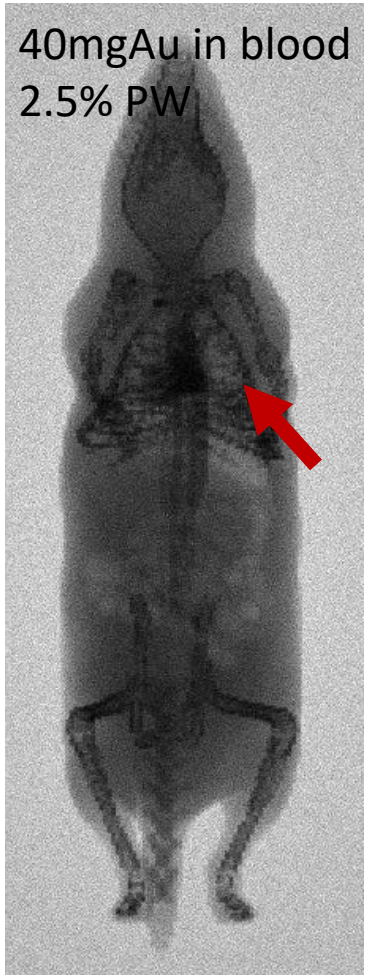


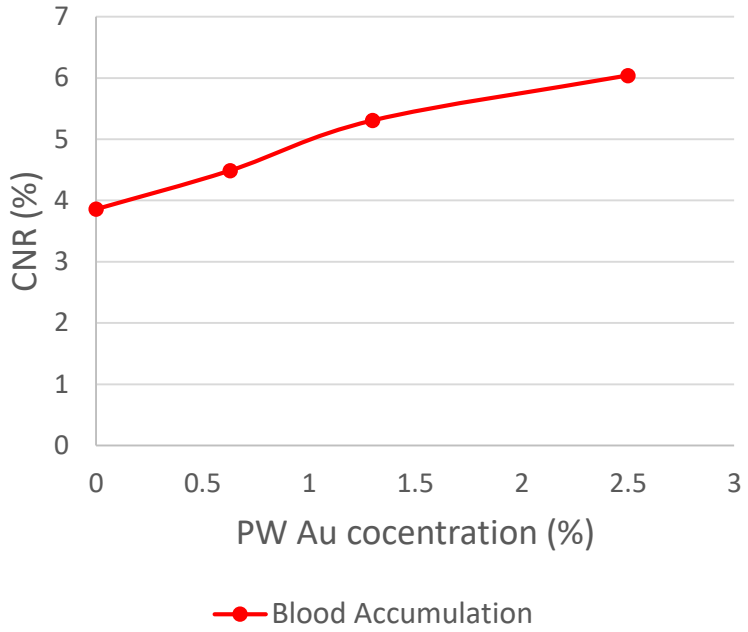
2. Full Accumulation in the bloodstream











- No veins in MOBY mouse phantom – blood only visible in the heart
- Typical mouse blood volume taken into account for PW concentration

3. Bio distribution by D. James et al (2007) – 4hrs p.i.

Healthy female albino mice of >6 weeks age
About 15 g body mass
Anesthetized via isoflurane
Injected with 100µl of PEGylated nanoshells suspended in 0.9% NaCl via tail vein
Dose injected: 10µgAu/g of mice weight (0.15mgAu/mouse)
Concentrations for 4hrs post administration

Table 6 Biodistribution of PEG-coated 110/10 nm silica/gold nanoshells among mice organs at 4 h to 28 days after intravenous injection at a dose of 10 µg g^{-1} animal. Adapted from ref. 81

	Concentration of Au (µg g^{-1} organ)							
Time	Blood	Liver	Kidney	Spleen	Lung	Muscle	Brain	Bone
Control	0.0009	0.0007	0.0011	0.0174	0.0021	0.0230	0.0011	0.0049
4 h	313.7	103.8	52.22	952.2	88.58	3.796	7.187	9.531
1 day	29.17	311.8	27.61	1890	12.71	1.060	0.547	5.912
7 days	0.0187	313.4	21.49	2863	6.066	1.916	0.0684	7.319
14 days	0.0290	324.5	19.30	2039	3.738	0.779	0.0310	5.365
21 days	0.0430	252.0	23.53	1738	4.748	1.593	0.1243	8.333
28 days	0.0567	227.2	24.70	1703	3.781	1.023	0.0293	6.875

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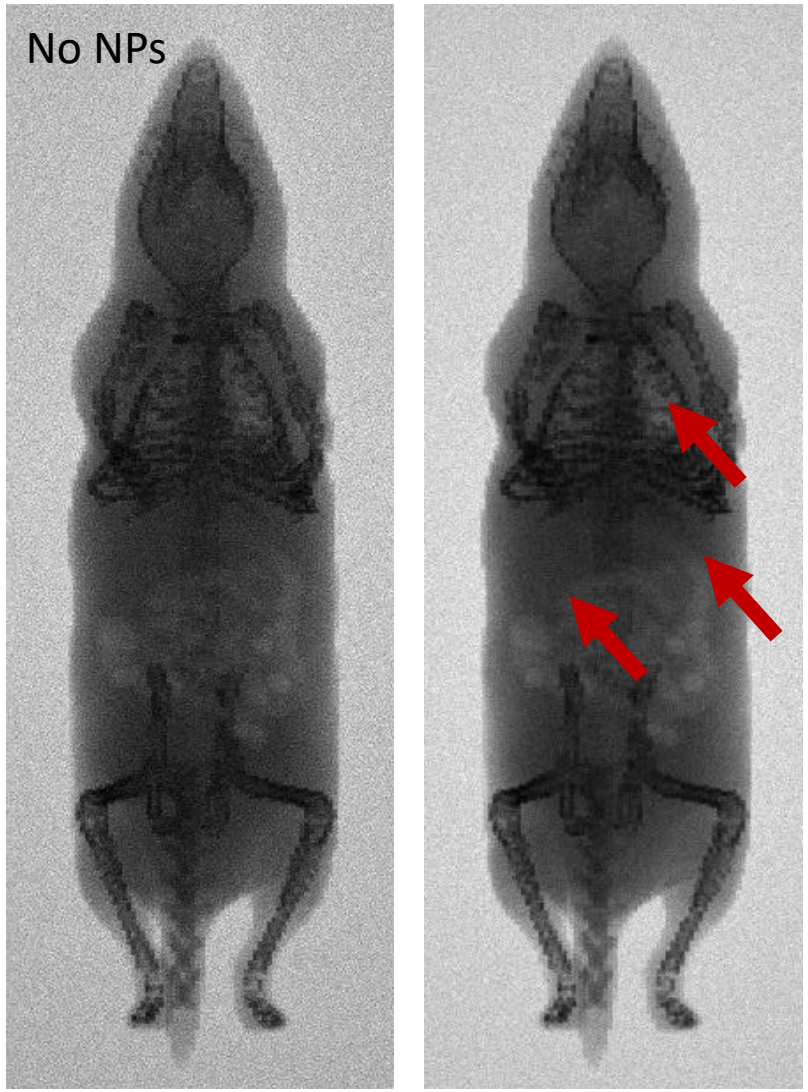
3. Bio distribution by D. James et al (2007) – 4hrs p.i.



Heart: 0.0314% PW
Liver: 0.104% PW
Spleen: 0.095% PW
all other organs < 0.01% PW

4. Bio distribution by D. James et al (2007) – 7 days p.i.

Healthy female albino mice of >6 weeks age
About 15 g body mass
Anesthetized via isoflurane
Injected with 100µl of PEGylated nanoshells suspended in 0.9% NaCl via tail vein
Dose injected: 10µgAu/g of mice weight (0.15mgAu/mouse)
Concentrations for 7 days post administration

Table 6 Biodistribution of PEG-coated 110/10 nm silica/gold nanoshells among mice organs at 4 h to 28 days after intravenous injection at a dose of 10 µg g^{-1} animal. Adapted from ref. 81

	Concentration of Au (µg g^{-1} organ)							
Time	Blood	Liver	Kidney	Spleen	Lung	Muscle	Brain	Bone
Control	0.0009	0.0007	0.0011	0.0174	0.0021	0.0230	0.0011	0.0049
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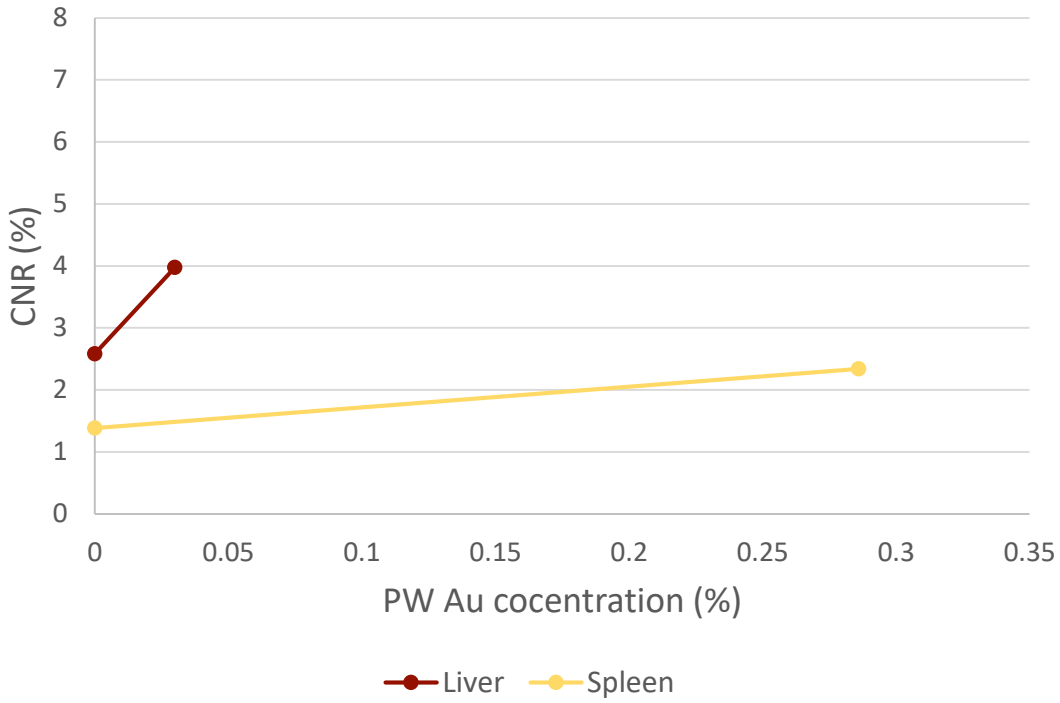
4. Bio distribution by D. James et al (2007) – 7 days p.i.

Liver: 0.03% PW
Spleen: 0.286% PW
all other organs < 0.01% PW



5. Bio distribution by J. Hainfeld et al (2004)

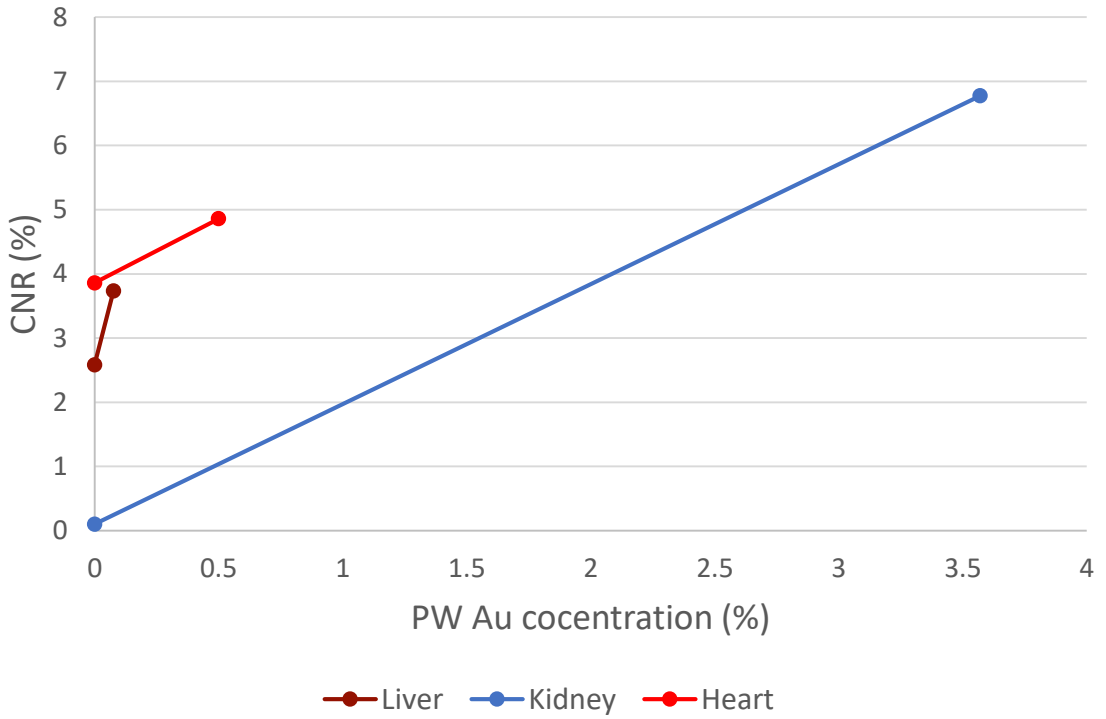
Balb/C mice injected subcutaneously with EMT-6 syngeneic mammary carcinoma cells
Injected with 1.9nm GNPs (Nanoprobes) – concentration of
Dosage: 1.35gAu/kg (appr. 27mg Au for 20g mouse) – in 0.01ml/g mouse

Table 1. Biodistribution of gold 5 min post i.v. injection of 1.35 g Au/kg.

	% injected dose/g	Tumour-to-tissue ratio	Tumour periphery-to-tissue ratio
Tumour	4.9 ± 0.6	1.0	1.8
Tumour periphery	8.9 ± 3.2	0.6	1.0
Muscle	1.4 ± 0.1	3.5	6.4
Liver	2.8 ± 0.1	1.8	3.2
Kidney	132.0 ± 2.7	0.4	0.1
Blood	18.6 ± 3.7	0.3	0.5

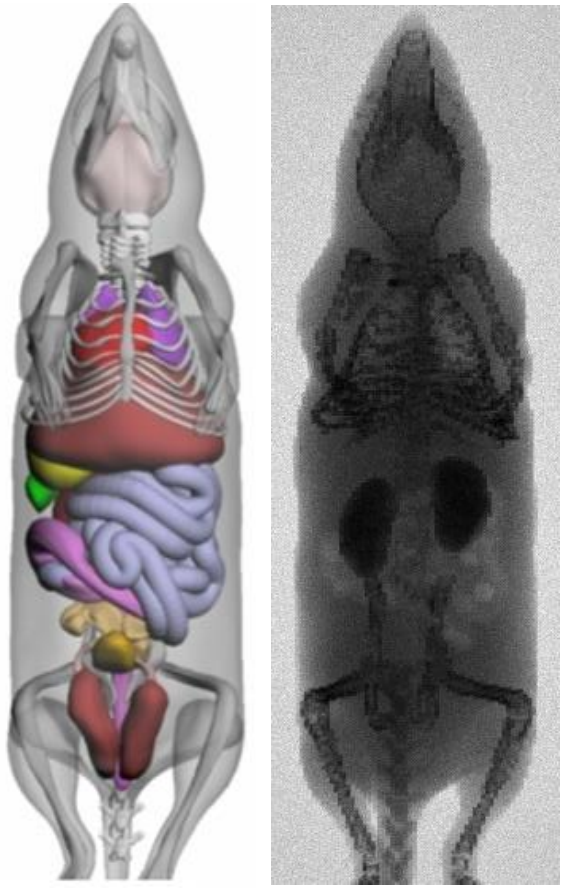
5. Bio distribution by J. Hainfeld et al (2004)

Liver: 0.076% PW
Kidney: 3.57% PW
Heart: 0.5% PW
all other organs < 0.01% PW



Overview and Next Steps

- A simulation platform for x-ray imaging studies with NPs has been developed and validated
- Both phantom and in vivo imaging studies performed
- Possibility of other NPs solutions as well (e.g. magnetic NPs)
- Gives the possibility to optimize imaging protocols and thus reduce the number of animals needed for an in vivo x-ray imaging study with NPs



Overview and Next Steps

- A simulation platform for x-ray imaging studies with NPs has been developed and validated
- Both phantom and in vivo imaging studies performed
- Possibility of other NPs solutions (e.g. magnetic NPs)
- Possibility to optimize imaging protocols and reduce the number of animals needed for in vivo NPs imaging study

NEXT STEP:

- Expand the platform to simulate tomographic x-ray imaging too (Computed Tomography) and validate it through Hus
- Use it to explore advanced imaging techniques (e.g. Dual Energy)