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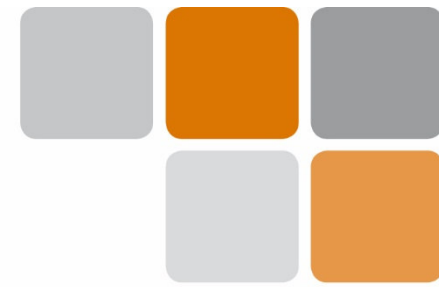


Photo-activation therapy with high-Z nanoparticles : modelling at a micrometer level and experimental comparison

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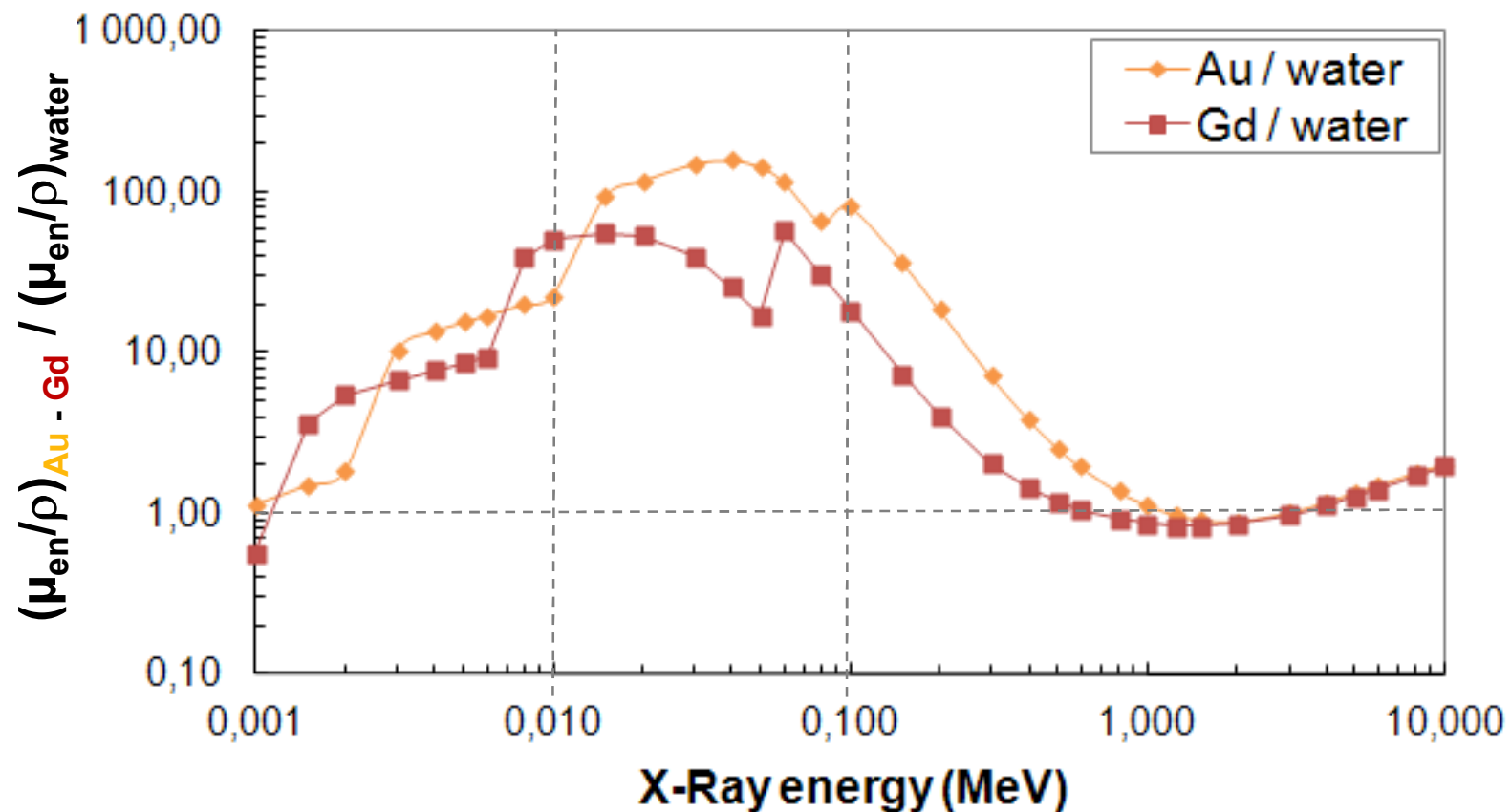
Monday 27th February 2012



- Context and objectives
- Simulation results
- Experimental comparison
- Conclusions and Prospects

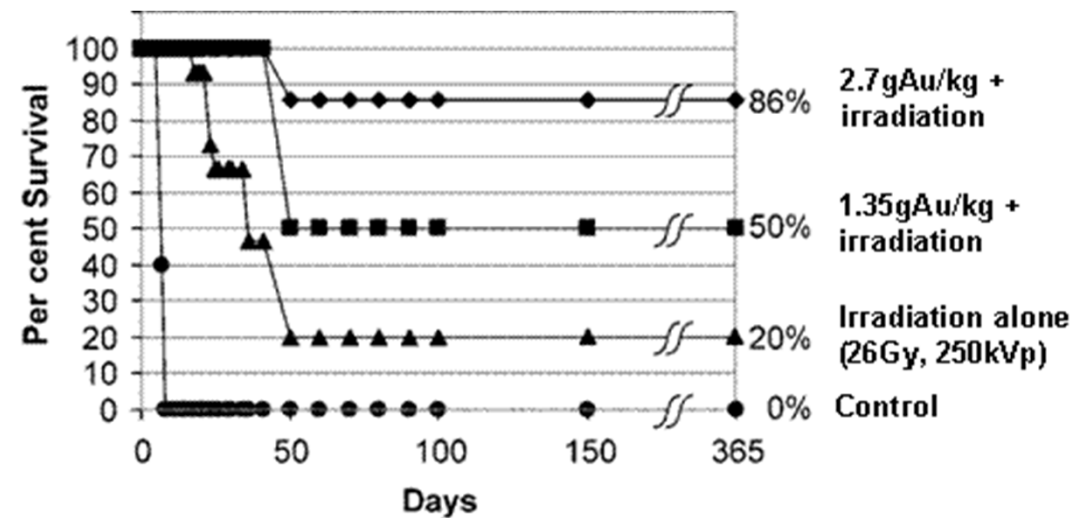
- **Photo-activation therapy** : combines low energy X-ray beams with high-Z elements (iodine, gold, gadolinium, platinum...).

Ratio of X-ray mass energy-absorption coefficients Gd or Au / water (NIST)



- Technique started with iodinated contrast agents (*Norman et al, Radiology (1978)*).

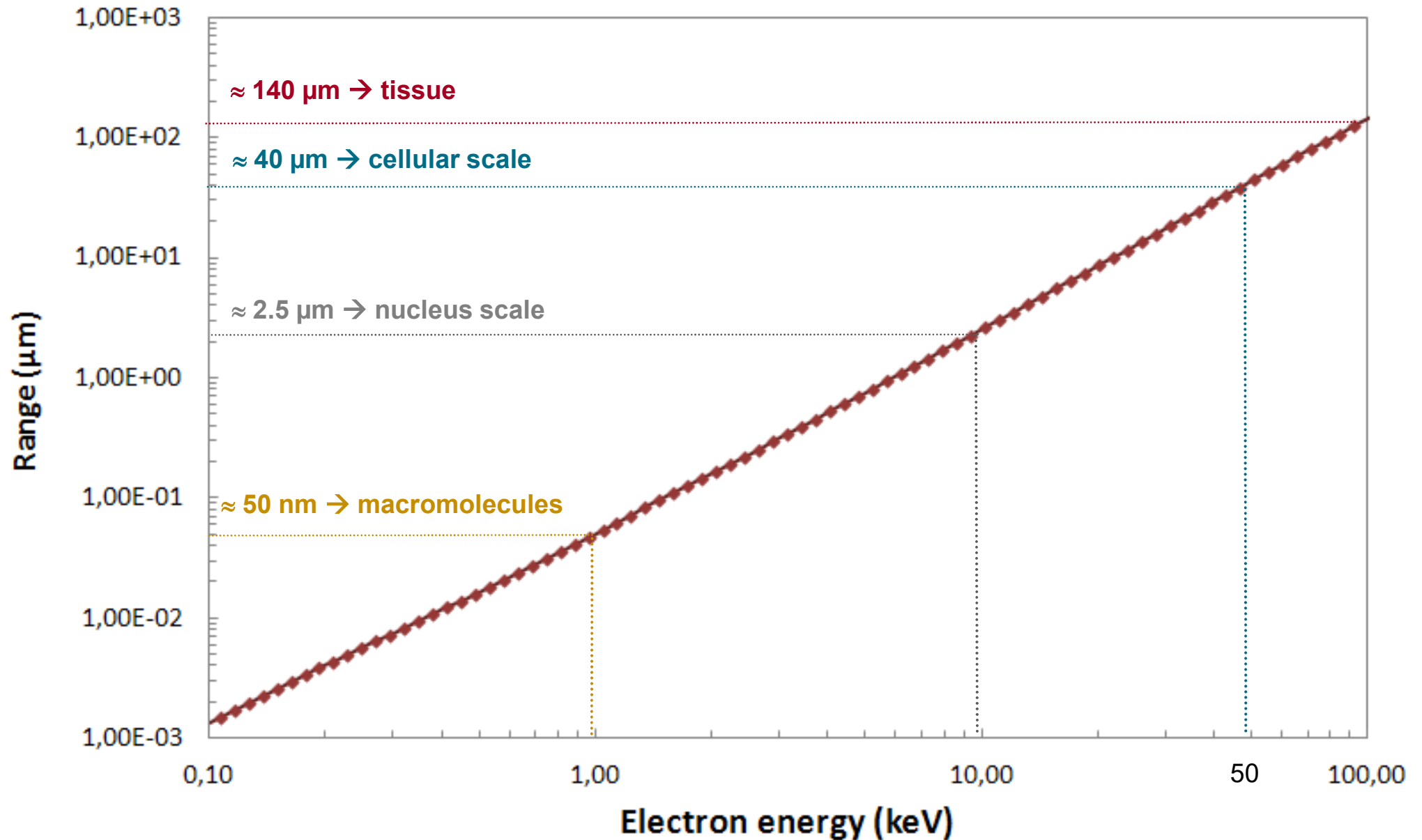
- Hainfeld et al. (*Phys. Med. Biol. (2004)*) : Survival response up to a factor of 4, treating cancerous mice with **gold-nanoparticles (AuNP)** of 1.9nm (RX tube at 250kVp).



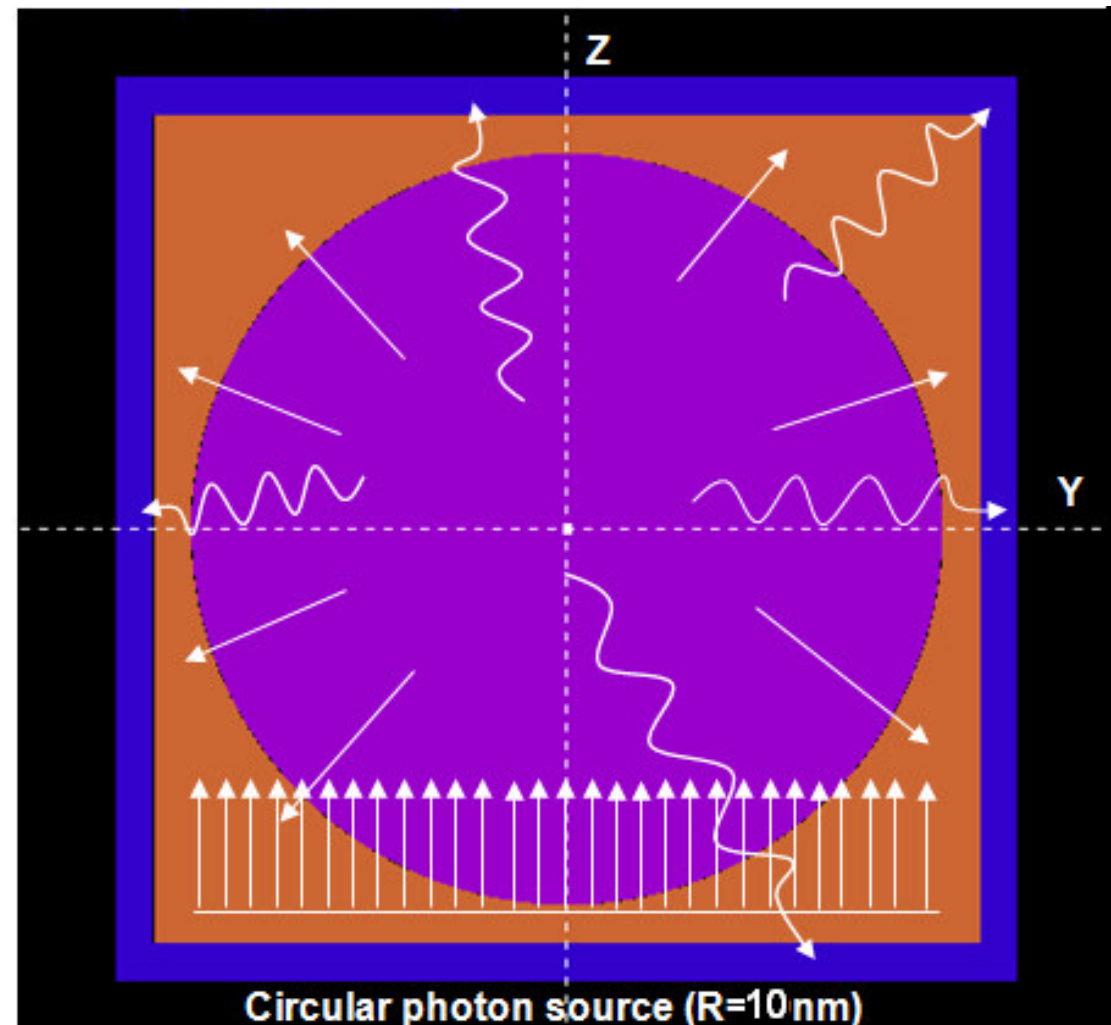
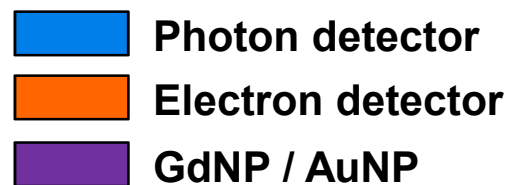
- Cho et al. (*Phys. Med. Biol. (2005)*): **Monte Carlo** calculation of tumour dose enhancement with homogeneous gold up to a factor of 2.1 with Hainfeld's conditions.
- Such radiobiological enhancement not explained by macroscopic physical model. Modelling at the **lower scale**.

- Objectives, Monte Carlo simulations :
 - **Gold and gadolinium nanoparticles** (AuNP & GdNP) : dose and electron spectra emitted from NP.
 - **Unicellular geometry with gadolinium** : comparison with experiments made at ESRF (*European Synchrotron Radiation Facility*).
 - **Challenge** : find an appropriate physical observable to correlate with biological data.

Electron range in water (Penelope tables)

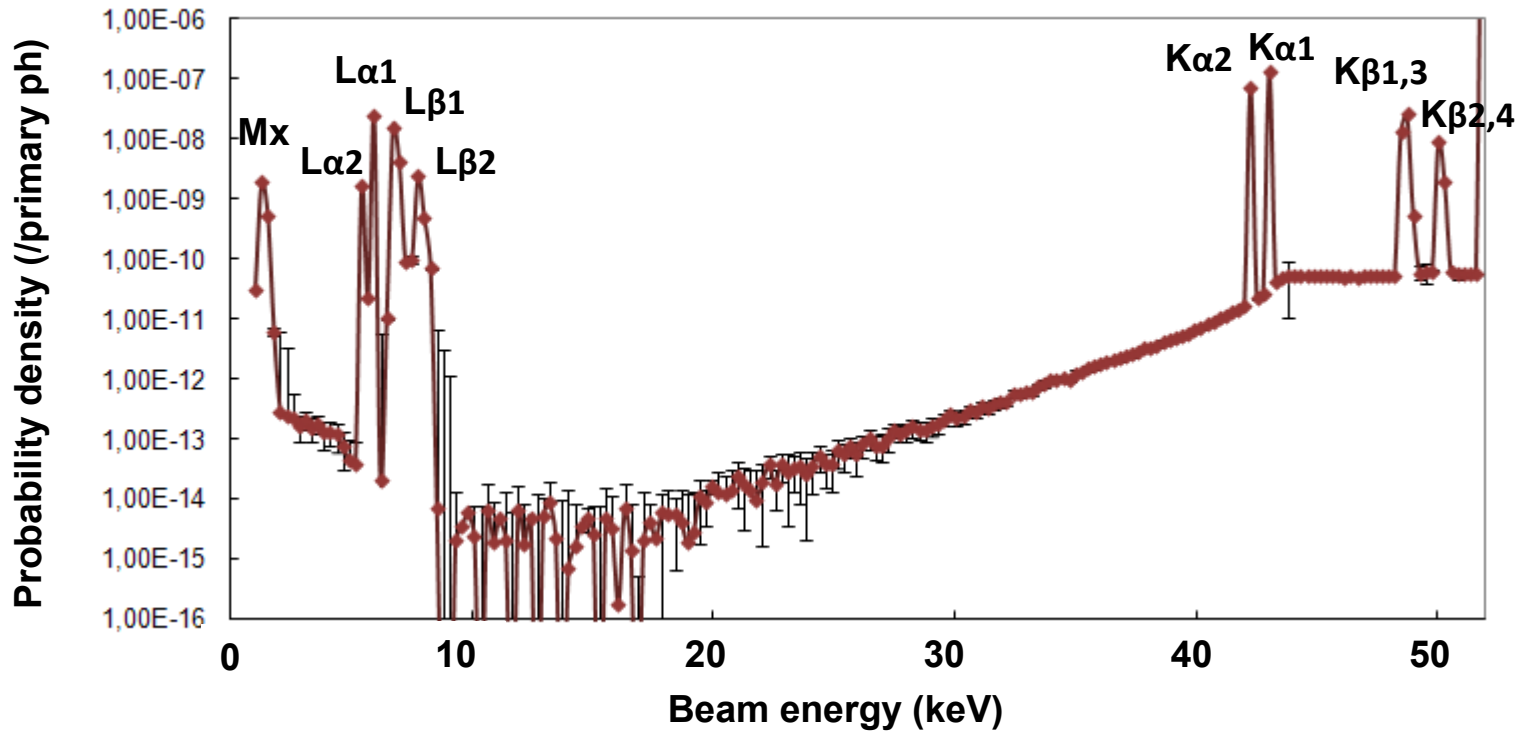


- **Penelope**: Monte Carlo code adapted for low energy electron and photon transport (lower limit of electron transport : 100 eV).
- First study : Dose deposition and spectra of secondary particles emitted from a single AuNP and GdNP.



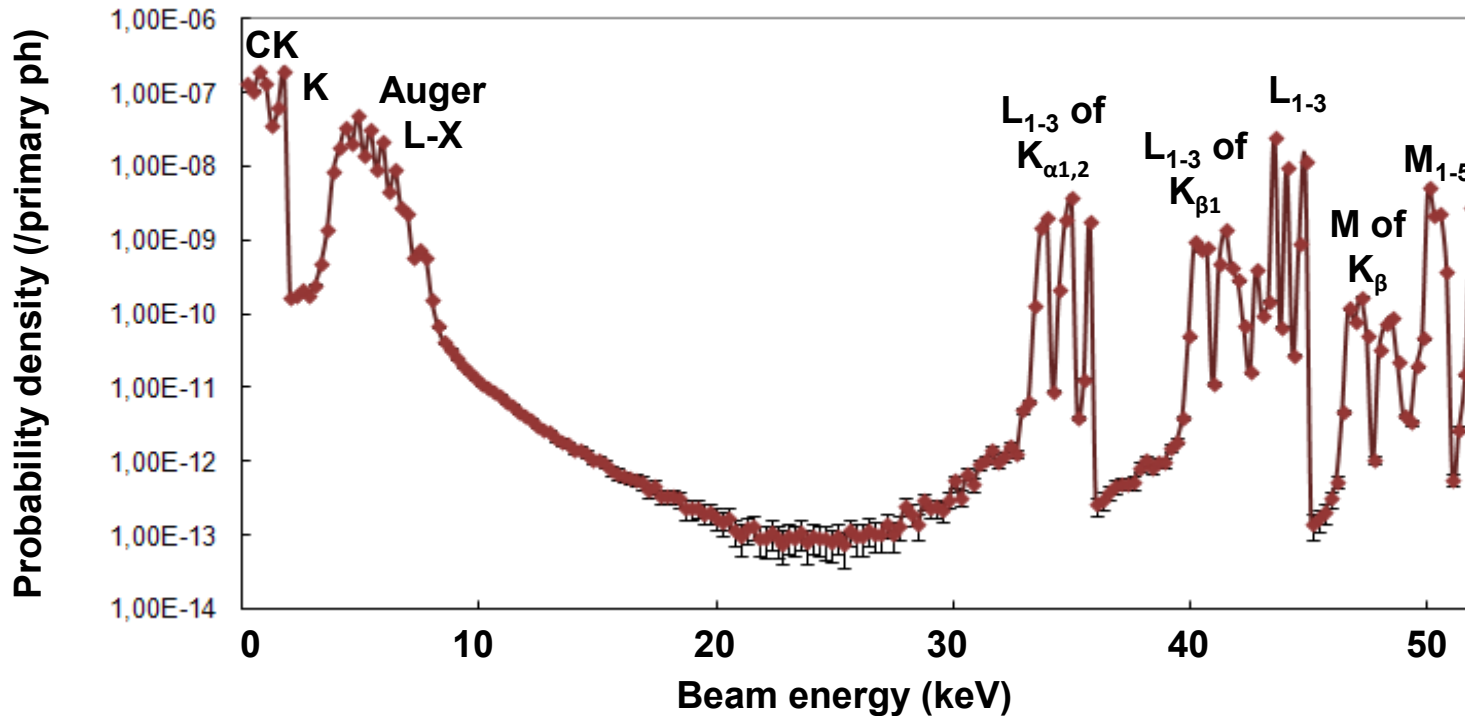
Simulation results Spectra from GdNP

Photon spectrum emitted from a GdNP of 10nm : 52 keV



- X-ray beam energy : 52 keV. Diameter of GdNP : 10 nm.
- Gd K-edge : 50.2 keV.
- Au K-edge : 80.7 keV.

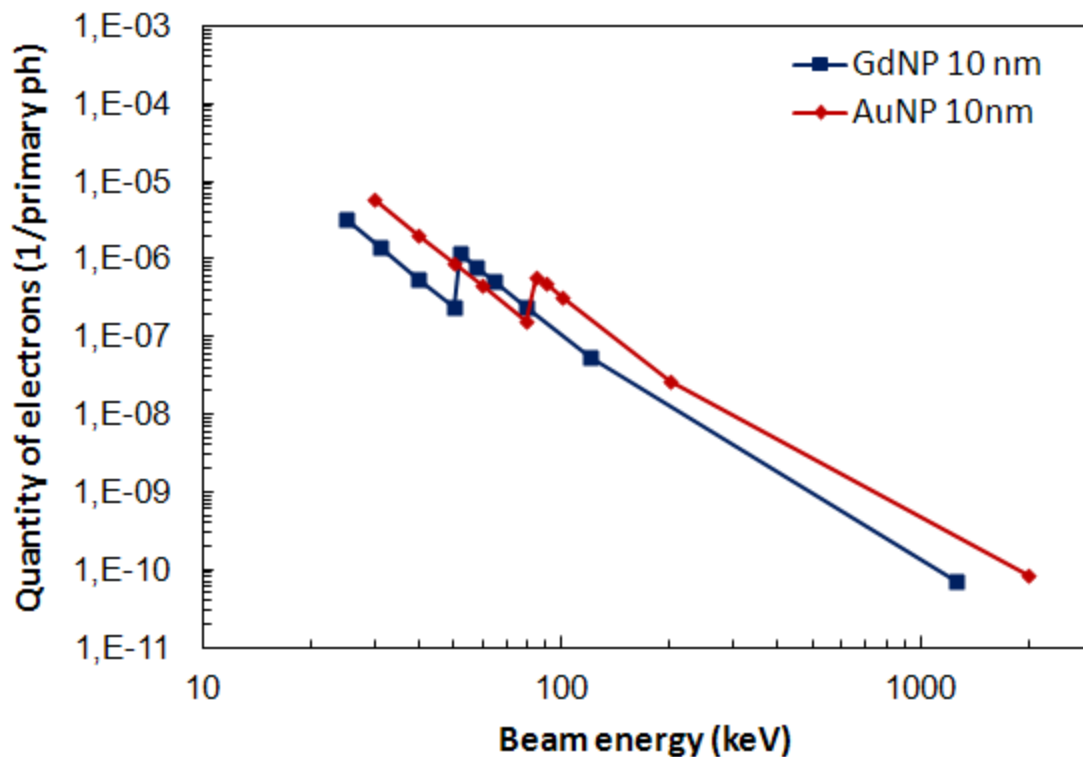
Electron spectrum emitted from a GdNP of 10nm : 52 keV



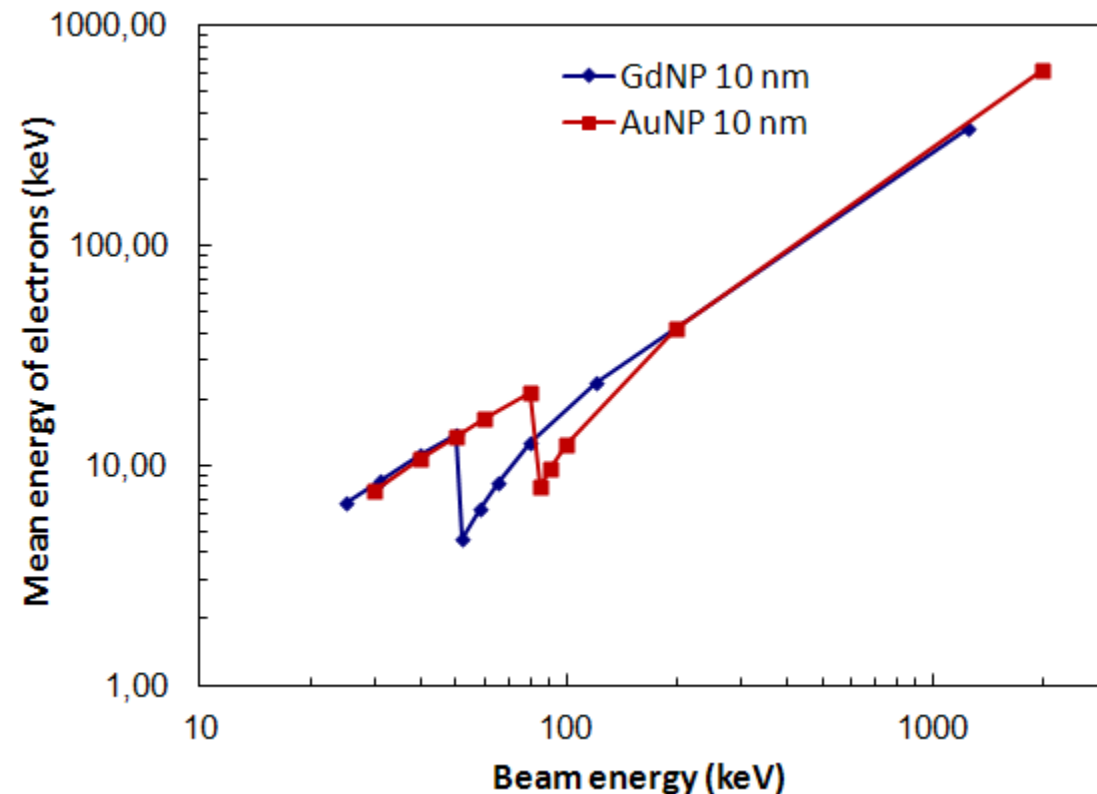
- Relaxation cascade and X-ray interaction with shell and sub-shell well described in Penelope.

- Electron spectra emitted from a 10 nm diameter AuNP and GdNP as a function of beam energy.

■ Quantity



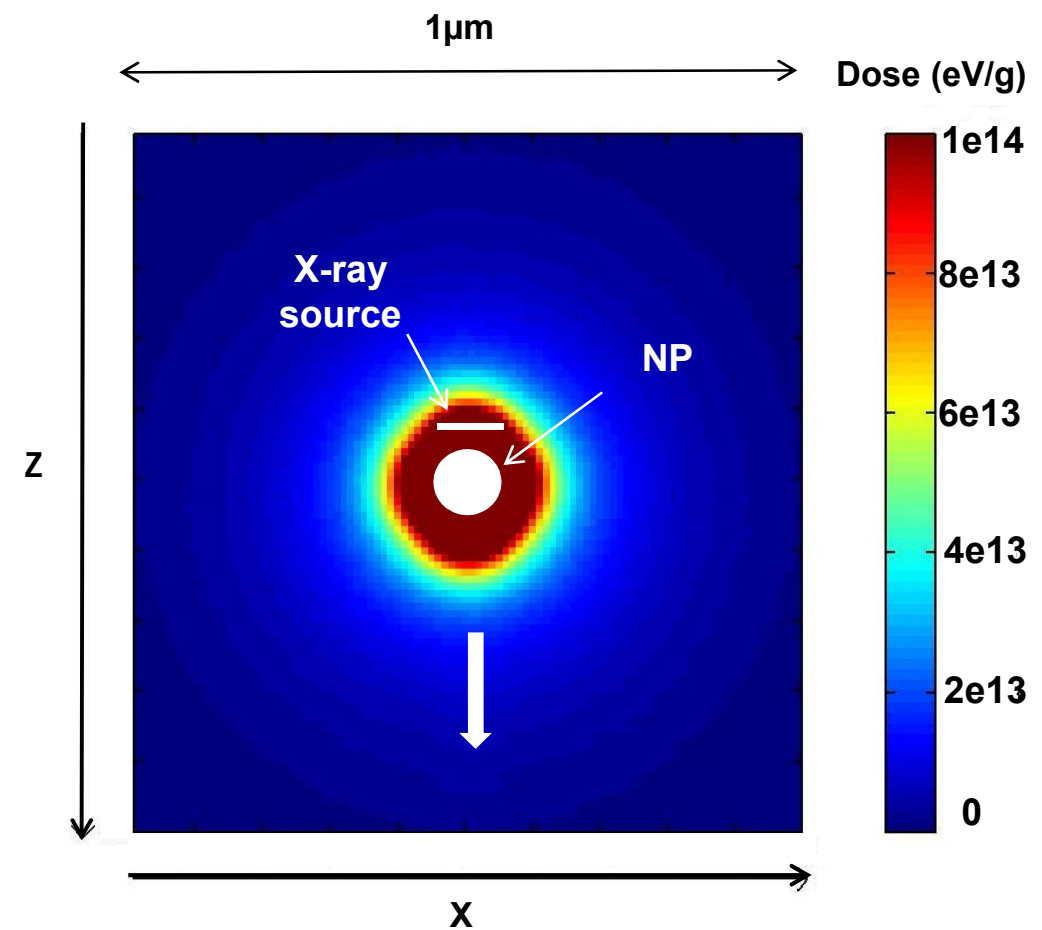
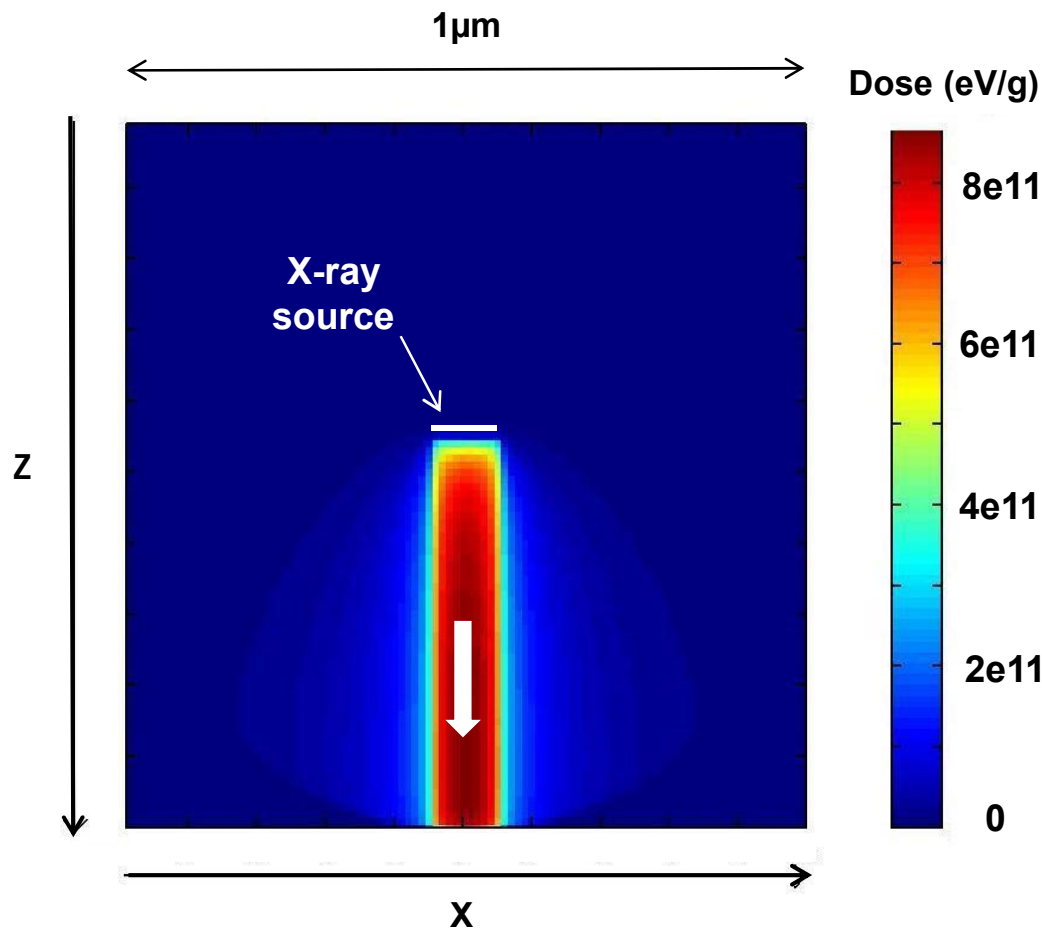
■ Mean energy



- More electrons produced in Gold except after the sharp Gadolinium K-edge.

- Mean energy lower after the Gd K-edge, provides a more “local” dose deposition.

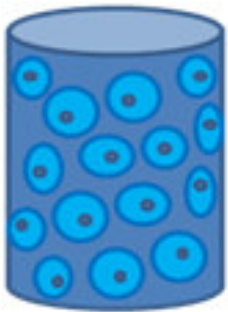
- Dose deposition at 500nm around a AuNP of 100nm with a 85 keV X-ray beam.
 - In water
 - With a centred AuNP



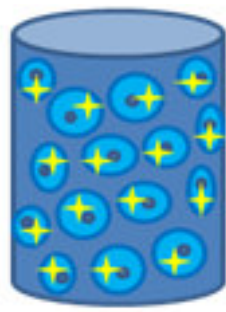
- AuNP : Increase of the dose up to a factor 100 with quasi-isotropic diffusion.

- **In vitro experiments** (ESRF, May/Sept 2011) : radiosensitivity on rat glioma cell line F98 with ultra small GdNP (*Angew. Chem. Int. Ed.* 2011).
 - Beam energies : 31, 49.5, 51, 65, 80 (synchrotron) and 1253 keV (Co60).
 - 5 experimental conditions :

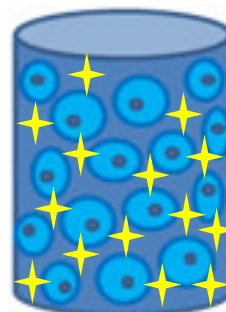
Control



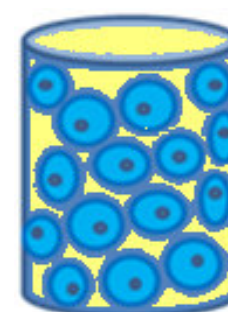
Internal GdNP



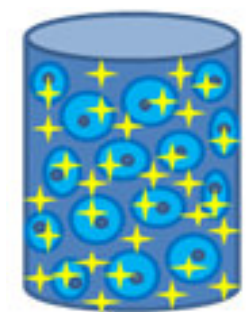
External GdNP



Magnevist



Internal & external
GdNP

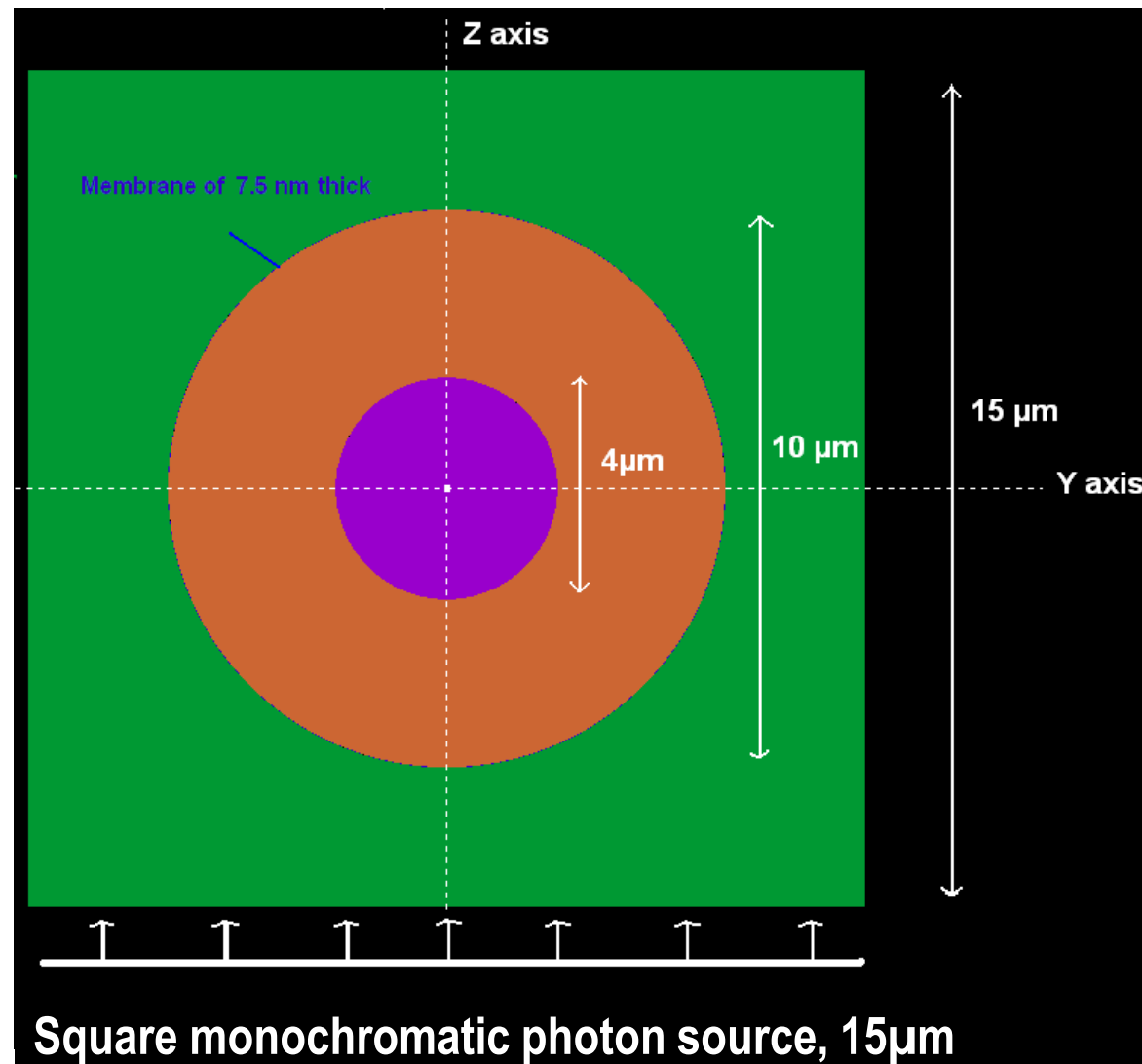
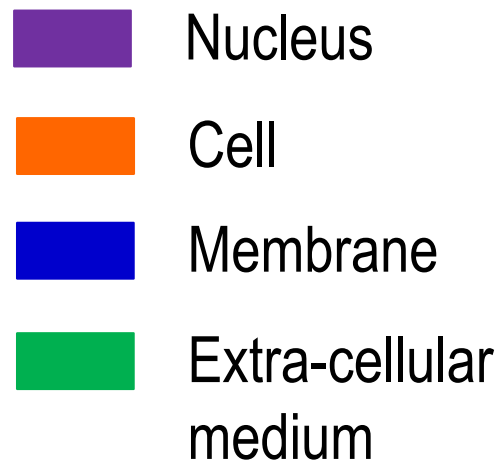


- Concentrations :
 - » Internal Gd : 0.6 mg/mL
 - » External Gd : 1.6 mg/mL

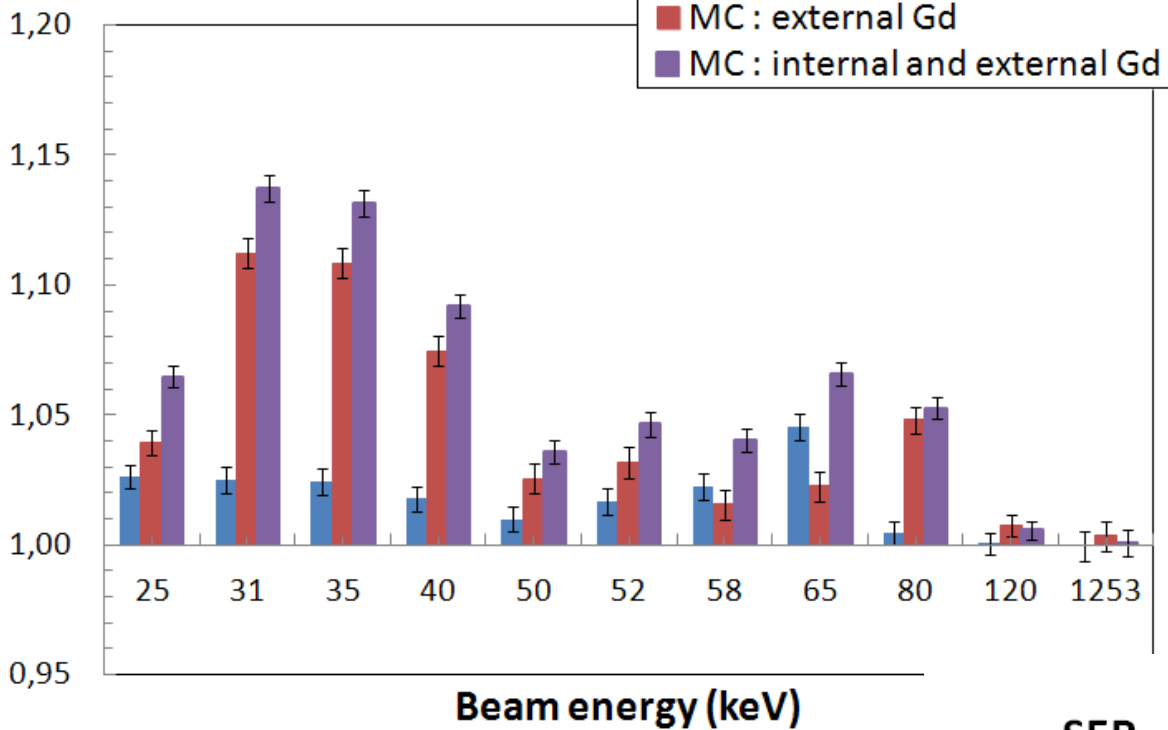
(cf. F. Taupin presentation on Friday)

- **Simulation** : Unicellular geometry.

Nanoparticles substituted with **homogeneous water-gadolinium mixture** localized into or outside the cell with the right Gd concentration.



Nucleus DEF



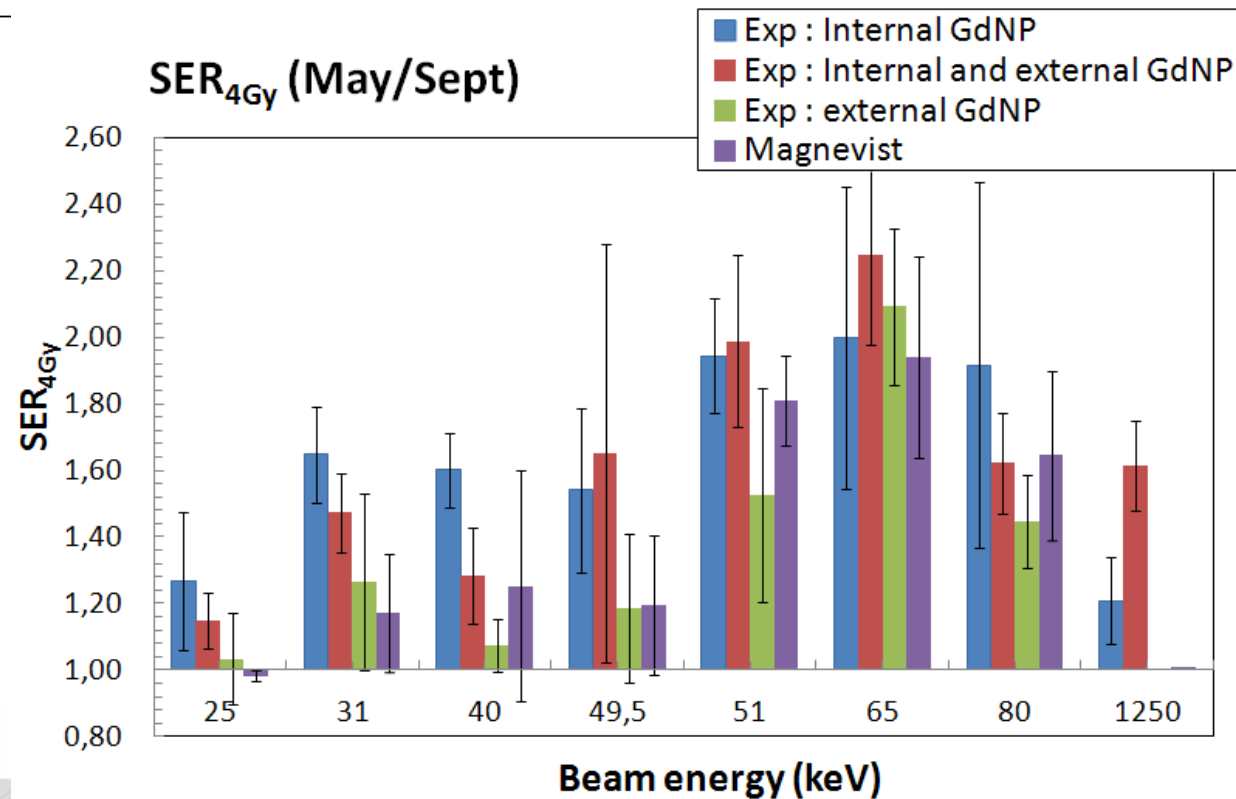
Experimental comparison Dose Enhancement Factor

$$DEF = \frac{\text{Dose (Gd)}}{\text{Dose (water)}}$$

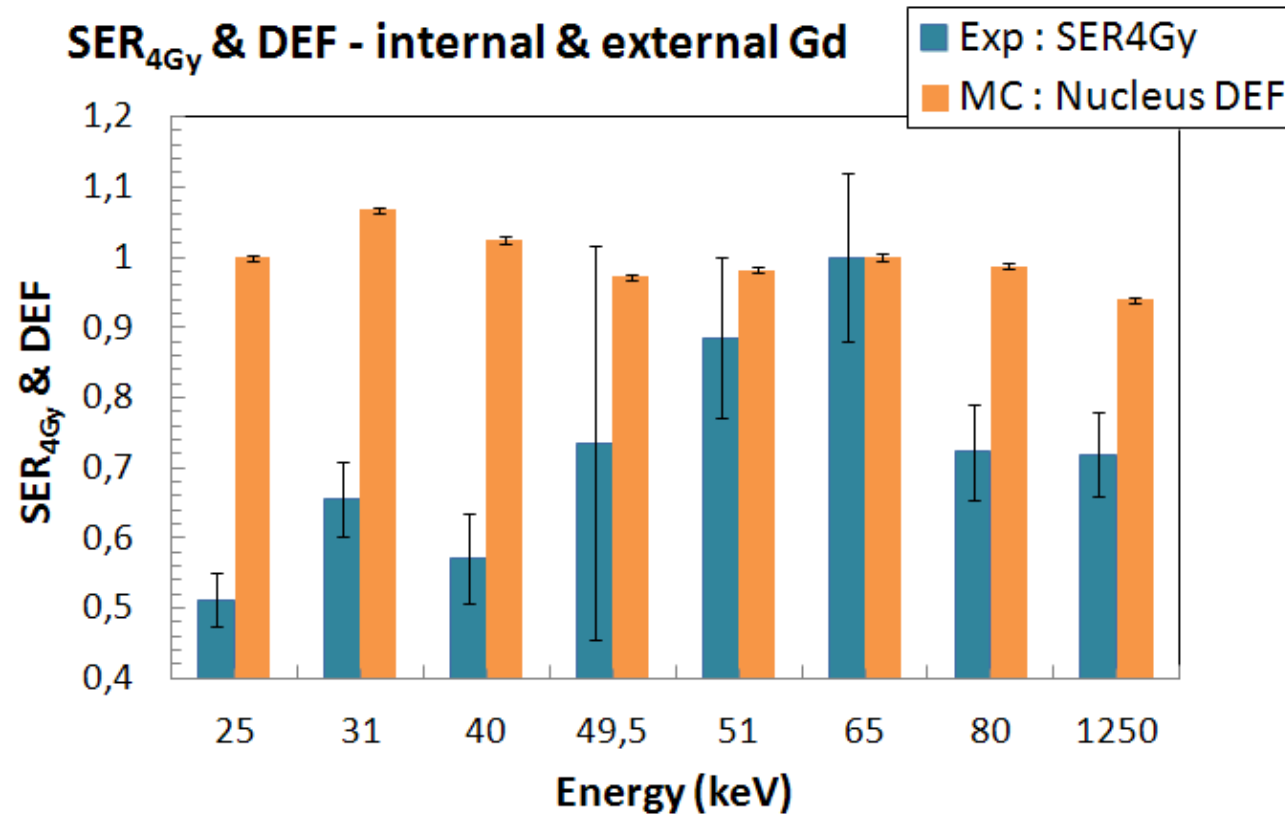
- Maximum DEF obtained of ~1.17 for internal and external Gd.

$$SER_{4GY} = \frac{\text{Survival at 4Gy (Gd)}}{\text{Survival at 4Gy (control)}}$$

- Experimental SER_{4GY} much higher (up to 2.25 for 65 keV).



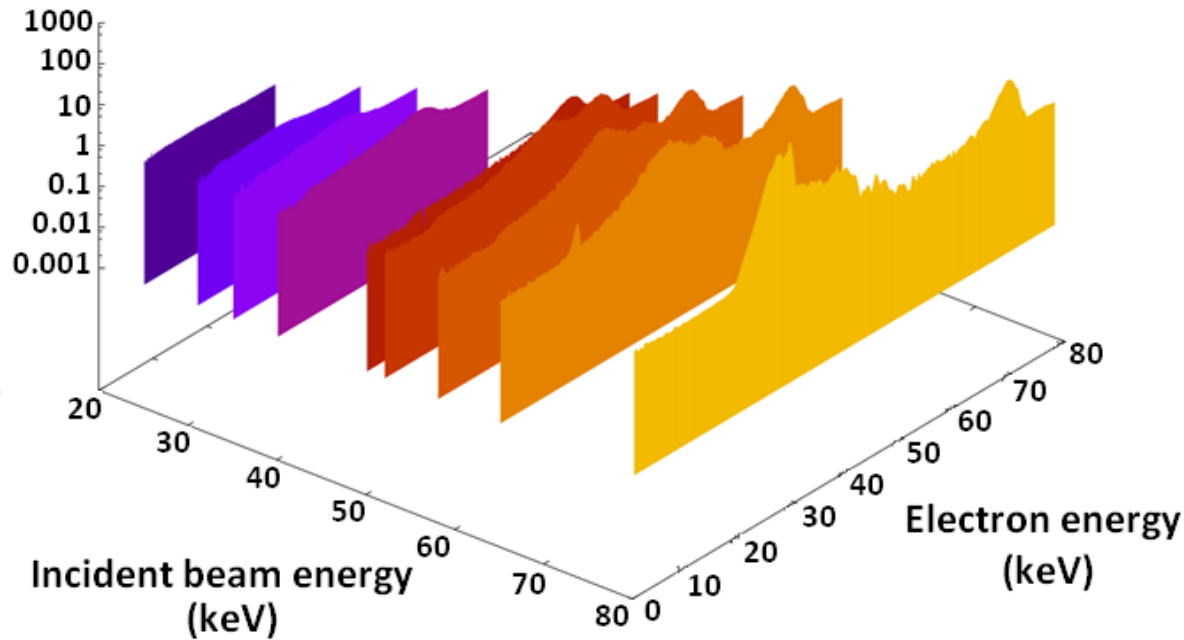
SER_{4Gy} & DEF - internal & external Gd



- Normalization at 65 keV to compare the tendency between the Nucleus DEF and SER_{4Gy}.
- Model and observable not well adapted for comparison with SER.
- Remarks :
 - Limited size of external volume.
 - Biological effects not limited to physical dose.

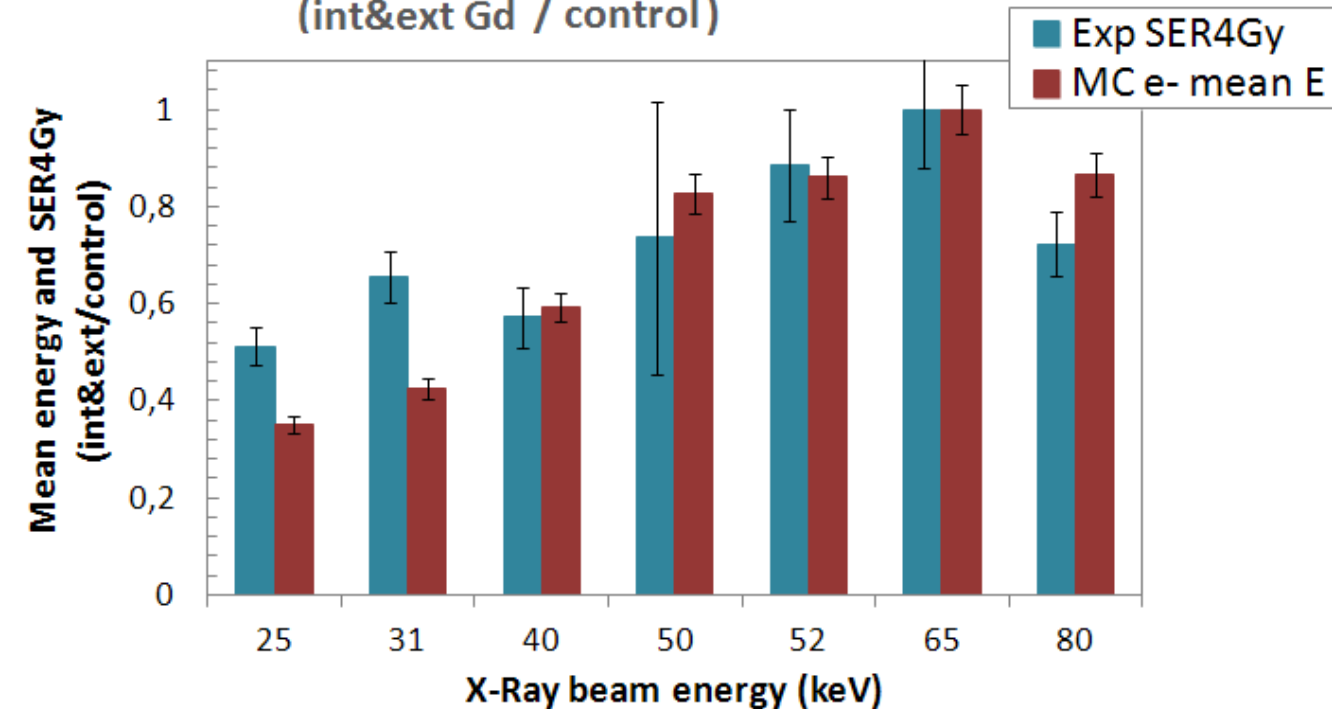
Experimental comparison Electron spectra incoming on nucleus

Probability density (int & ext Gd / water)



- Comparison of **electron spectra incoming on the nucleus** for all energies and conditions.

Mean energy of incoming e- and SER 4Gy
(int&ext Gd / control)



- Normalized at 65 keV :
Good correlation obtained.

- **Conclusions :**
 - Nanoparticle model : Study of secondary particles emitted under irradiation for different beam energies and comparison Gd/Au.
 - Unicellular model : calculation of DEF and electron spectra incoming on the nucleus for different conditions.
 - Comparison with experimental data : encouraging results but the model needs to be improved.
 - Separate intrinsic biological effects and physical effects.
- **Prospects :**
 - Model nanostructures in cell and multicellular geometries with Geant4.
 - Access to more detailed track information's with Geant4 : provide other observables for experimental comparison.

- Supervisors :

- Mathieu AGELOU
- Christophe CHAMPION
- Hélène ELLEAUME

- Coworkers:

- Florence TAUPIN
- Mélanie FLAENDERS
- Jean-Luc RAVANAT

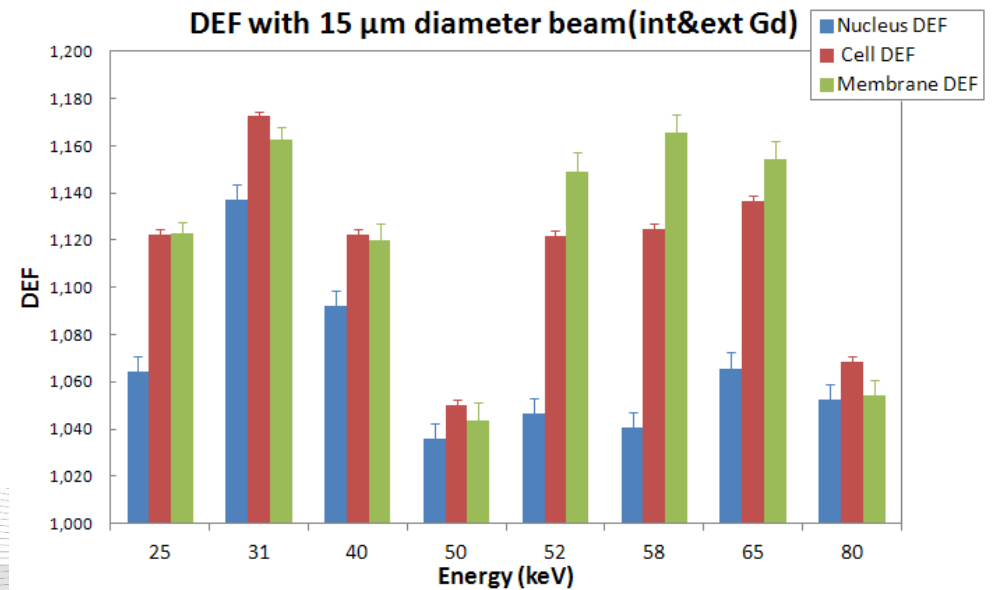
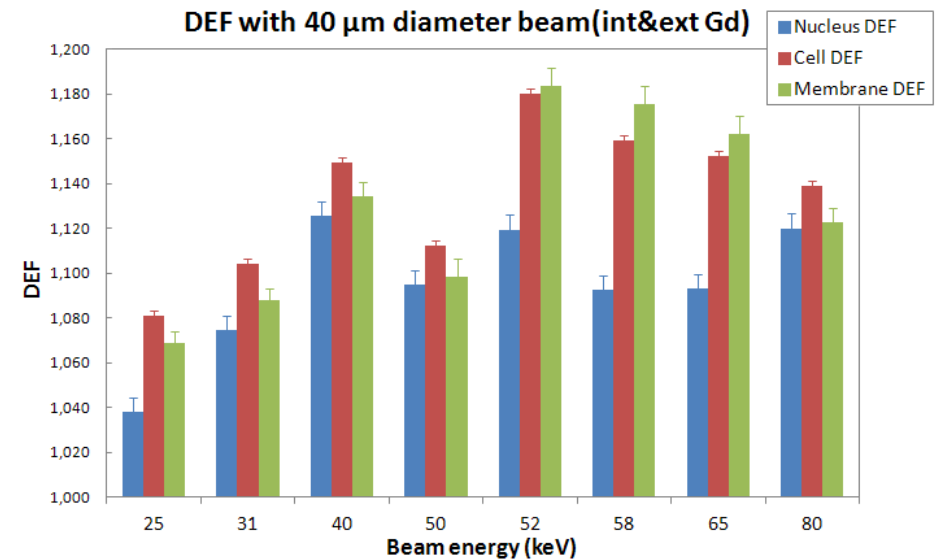
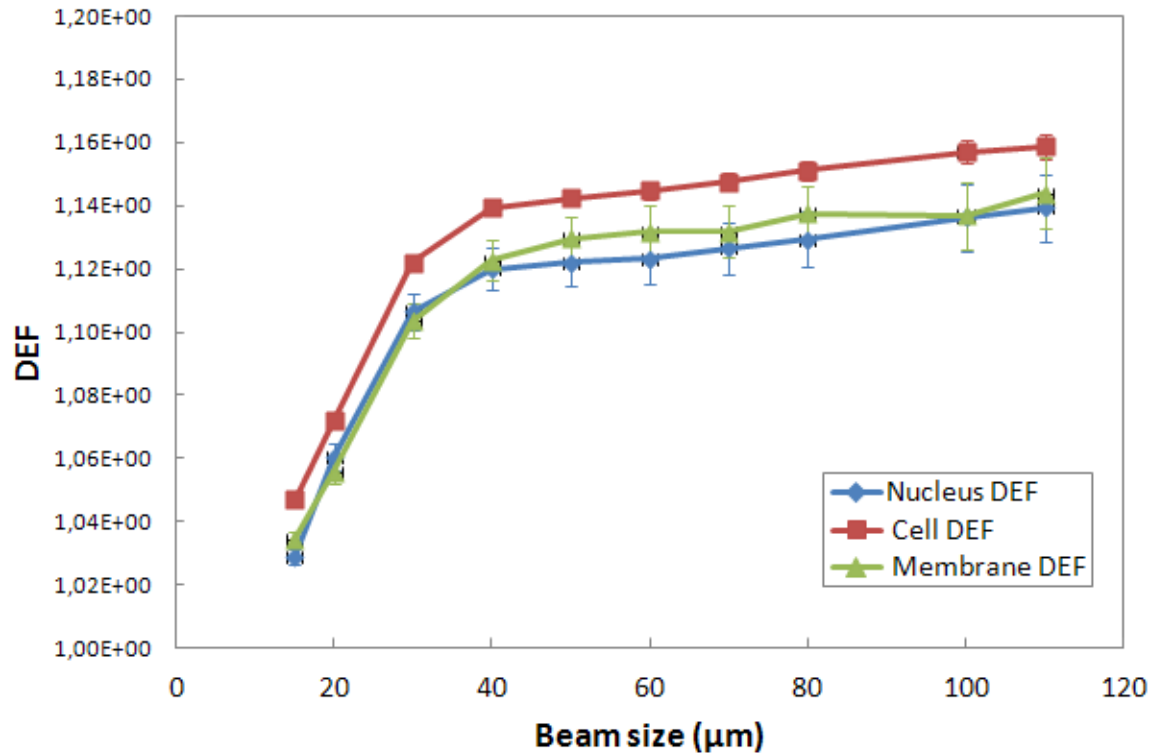


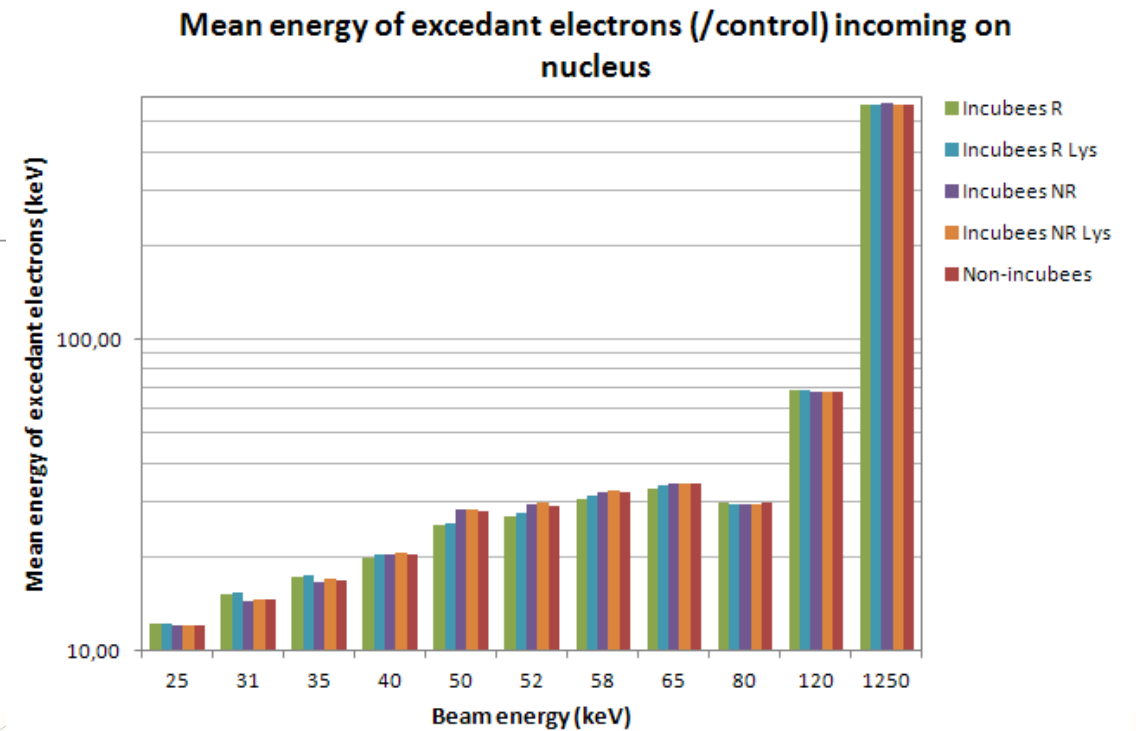
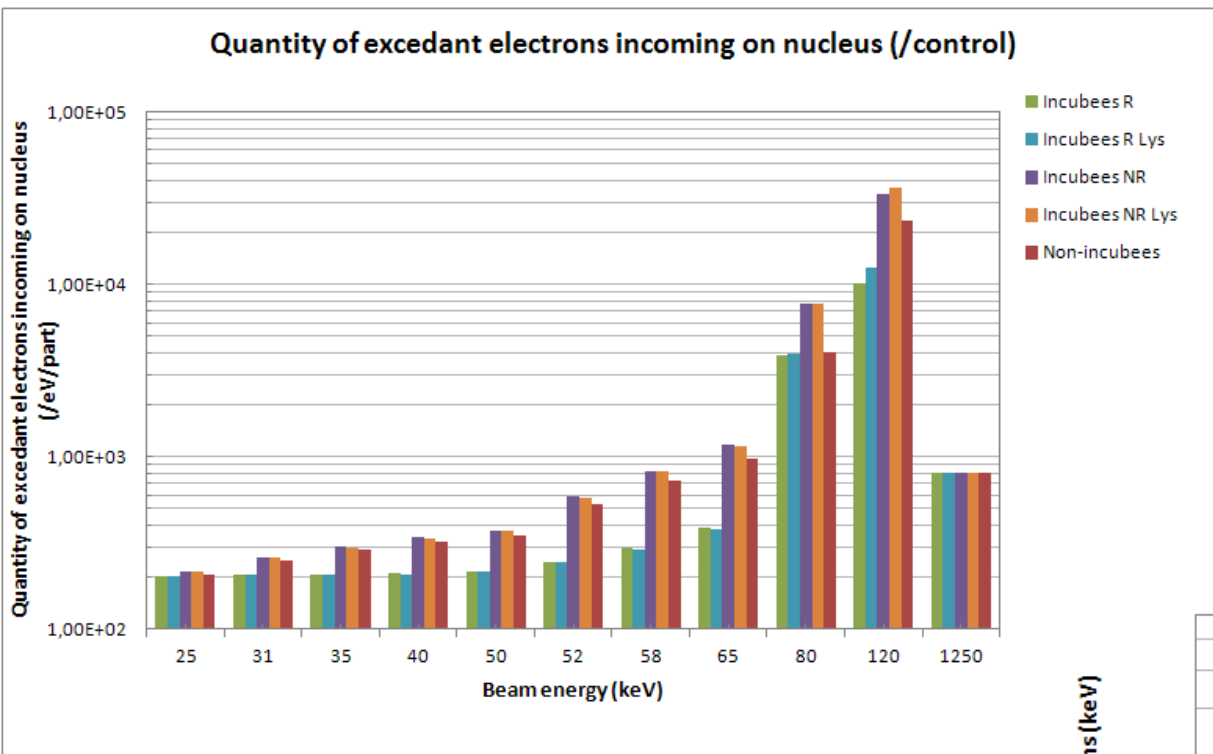
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- Study of the increase of the size of external volume for internal and external Gd condition. The X-ray beam size is equal to the external volume.

DEF as a function of the size of field for 80 keV





- Gd properties :
K-edge : 50.2 keV, Z : 64, density: 7.9 g/cm³
- Au properties :
K-edge : 80.7 keV, Z : 79, density: 19.3 g/cm³

- 1 μ m dose deposition of particles emitted from a AuNP as a function of energy and diameter:

