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

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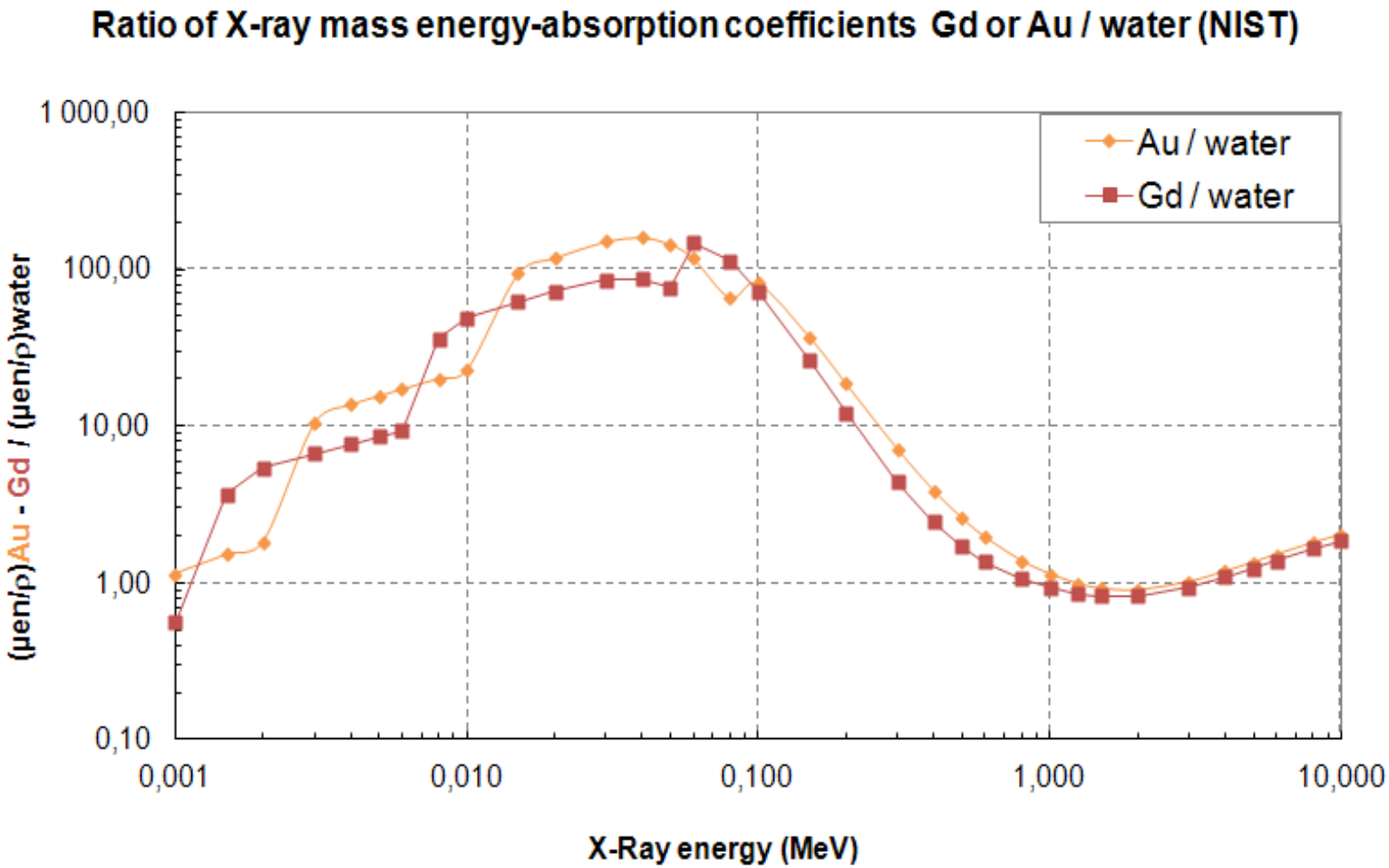
Summary

- Context and objectives
- Simulation results (PENELOPE)
- Experimental comparison
- Code comparison with GEANT4
- Conclusions and Prospects

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

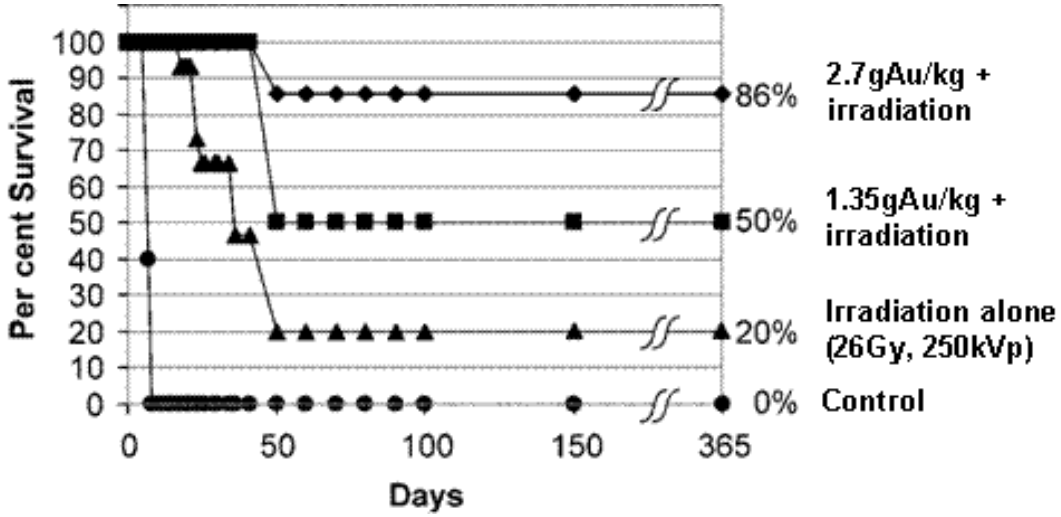


- Discovery of the radiosensitive effect due to the iodinated contrast products (ICP) in interventional radiology *(Norman et al, Radiology (1978))*.

- Studies continued by the team INSERM / ESRF: treatment of high grade gliomas *(clinical trial of phase I)*

  ICP : Enhancement factor ~ 2 (for 10 mg/ml). Do not integrate cells.

- 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).

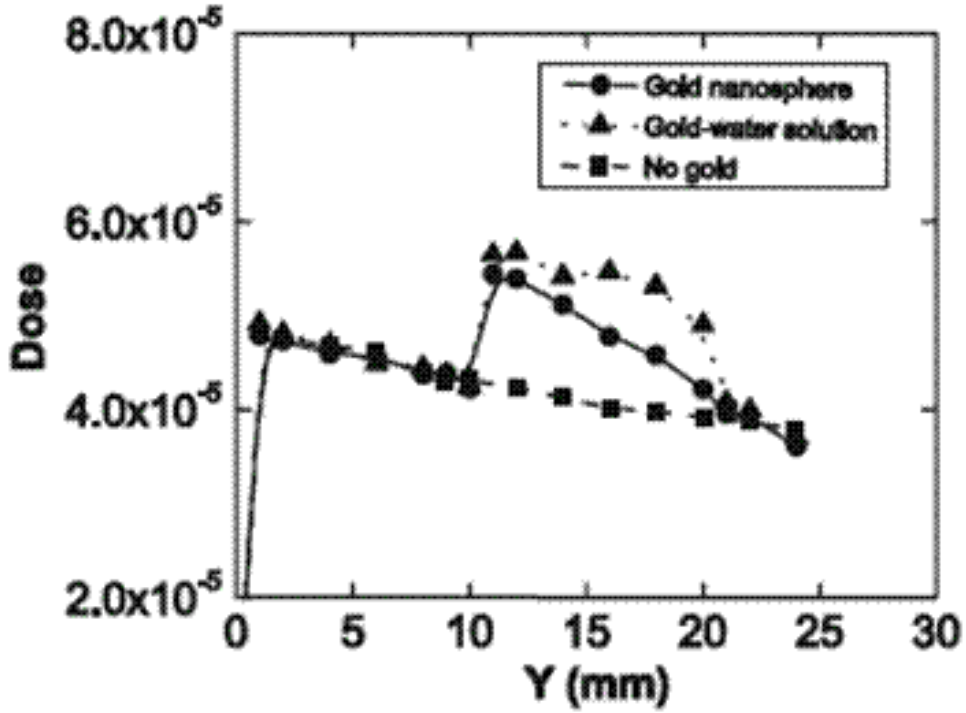


- Cho et al. *(Phys. Med. Biol. (2005))*: Monte Carlo calculation of tumour dose enhancement with homogeneous gold up to a factor of 2.1 with Hainfeld's conditions.

- Such radiobiological enhancement not explained by macroscopic physical model. Modelling at the lower scale.

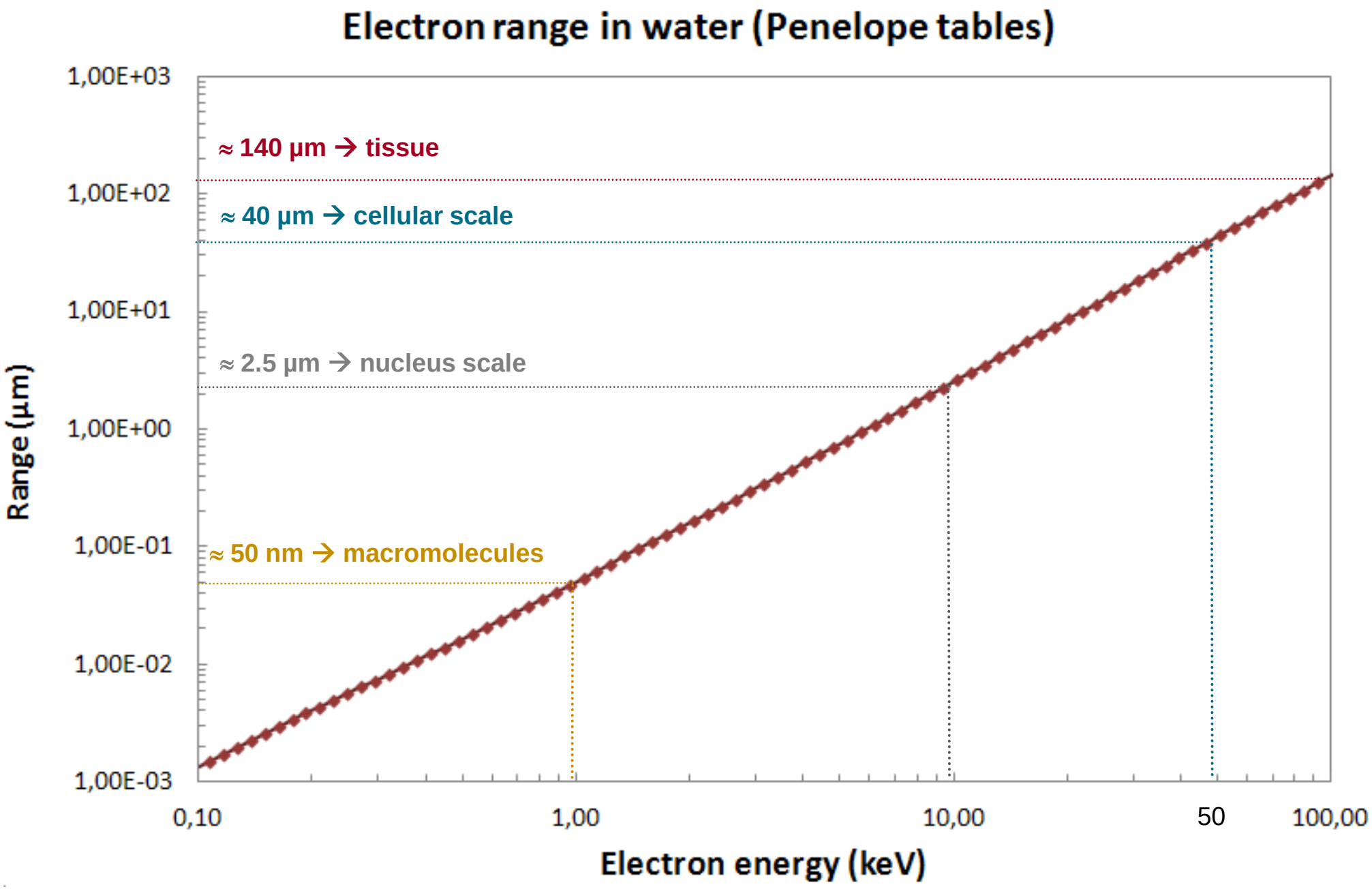
- Zhang et al. *(Biomed Microdevices (2009))* : Comparison of macroscopic dose calculations for a homogeneous gold-water model and nano-structured.

  Homogeneous case : overestimation of the dose up to 16%.



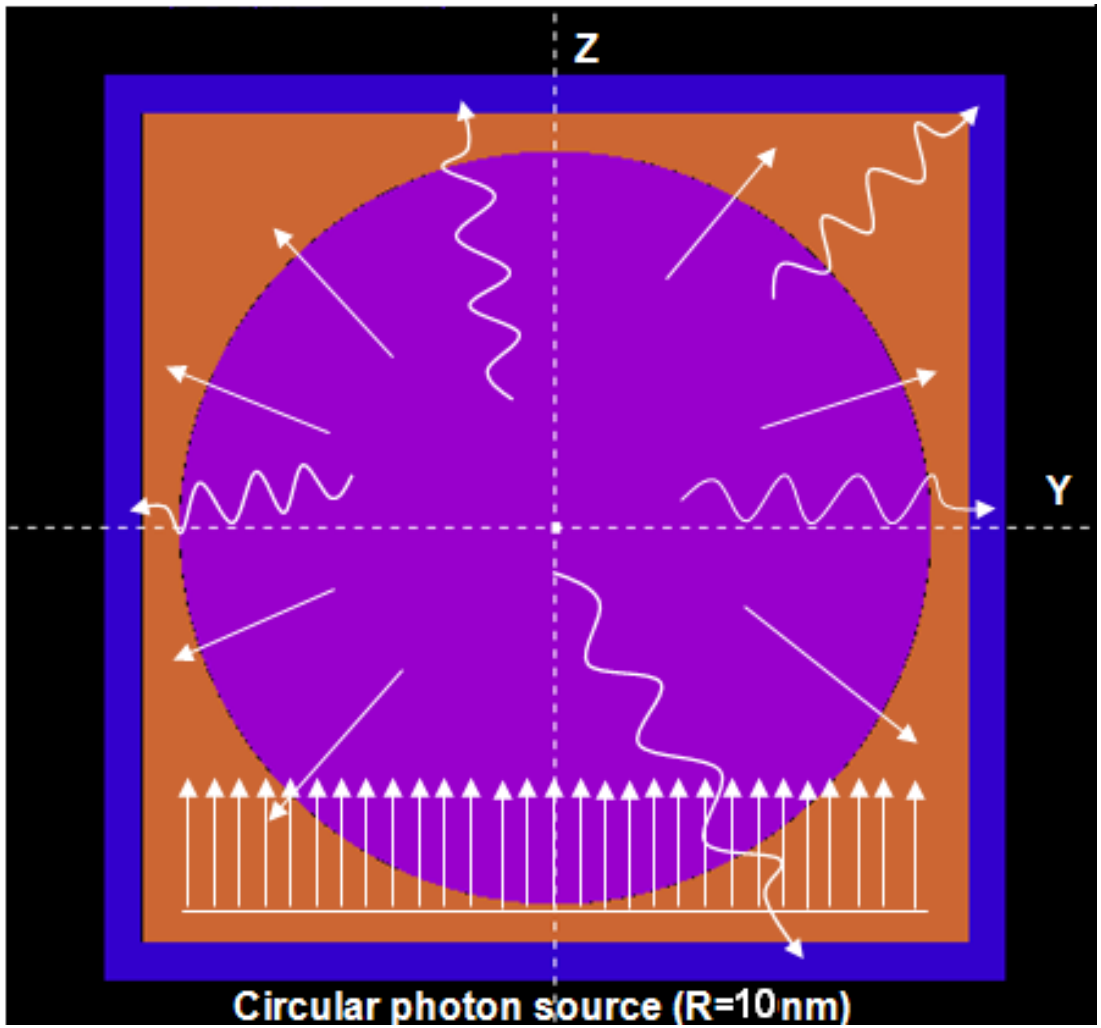
- Modelling the nanoparticles.

- Objectives, Monte Carlo simulations :
  - Challenge : find an appropriate physical observable to correlate with biological data.
  - Gold and gadolinium nanoparticles (AuNP & GdNP) : dose and electron spectra emitted from NP under irradiation *(PENELOPE)*.
  - Unicellular geometry with gadolinium : comparison with experiments made at ESRF (European Synchrotron Radiation Facility) *(PENELOPE)*.
  - Unicellular geometry with nanoparticles of gadolinium *(GEANT4)*.


Electron range in water (Penelope tables)
1,00E+03
1,00E+02
1,00E+01
1,00E+00
1,00E-01
1,00E-02
1,00E-03
Range (µm)
≈ 140 µm → tissue
≈ 40 µm → cellular scale
≈ 2.5 µm → nucleus scale
≈ 50 nm → macromolecules
0,10
1,00
10,00
50
100,00
Electron energy (keV)

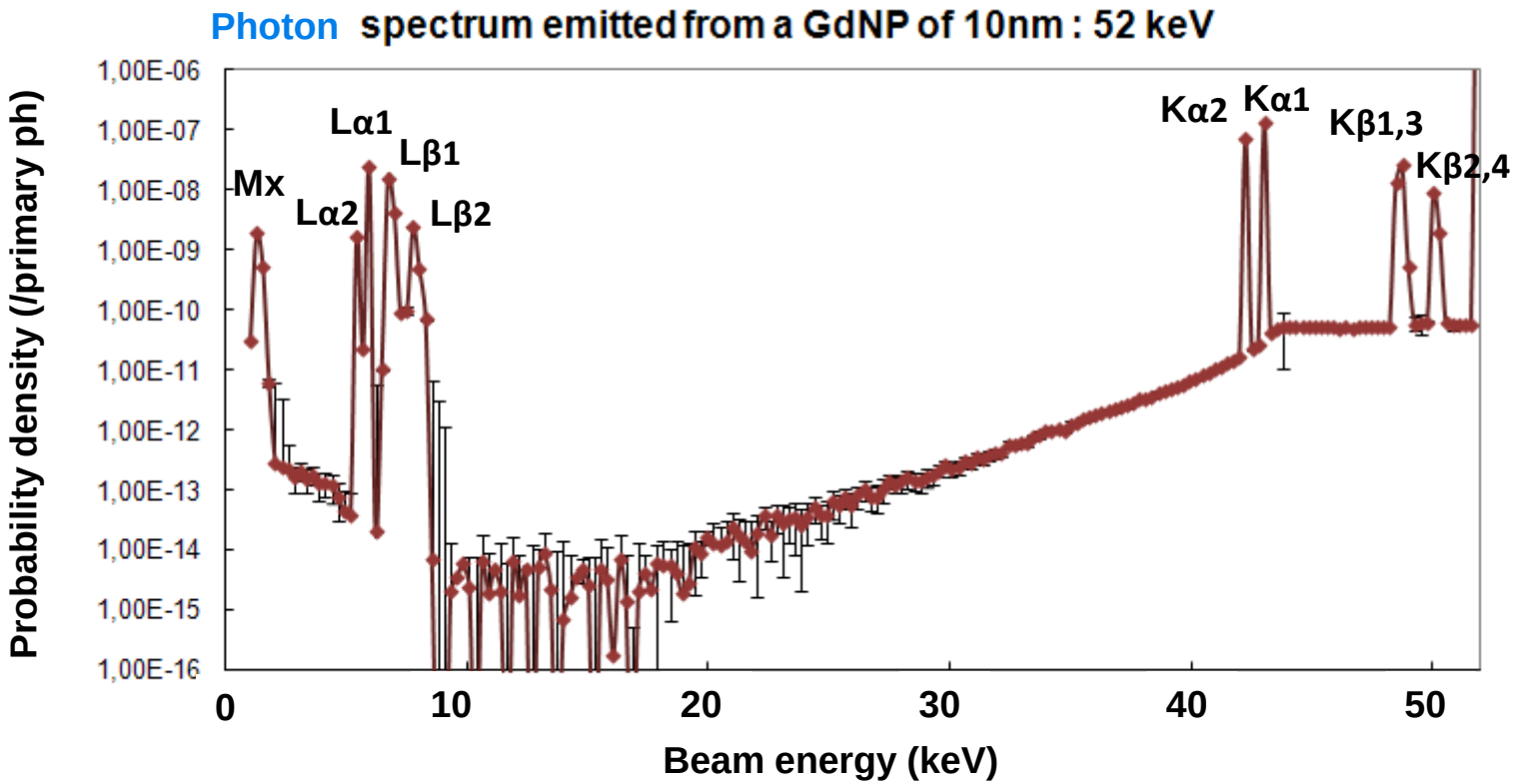
- PENELOPE : Monte Carlo code adapted for low energy electron and photon transport (lower limit of electron transport : 50 eV). Variance reductions ++.

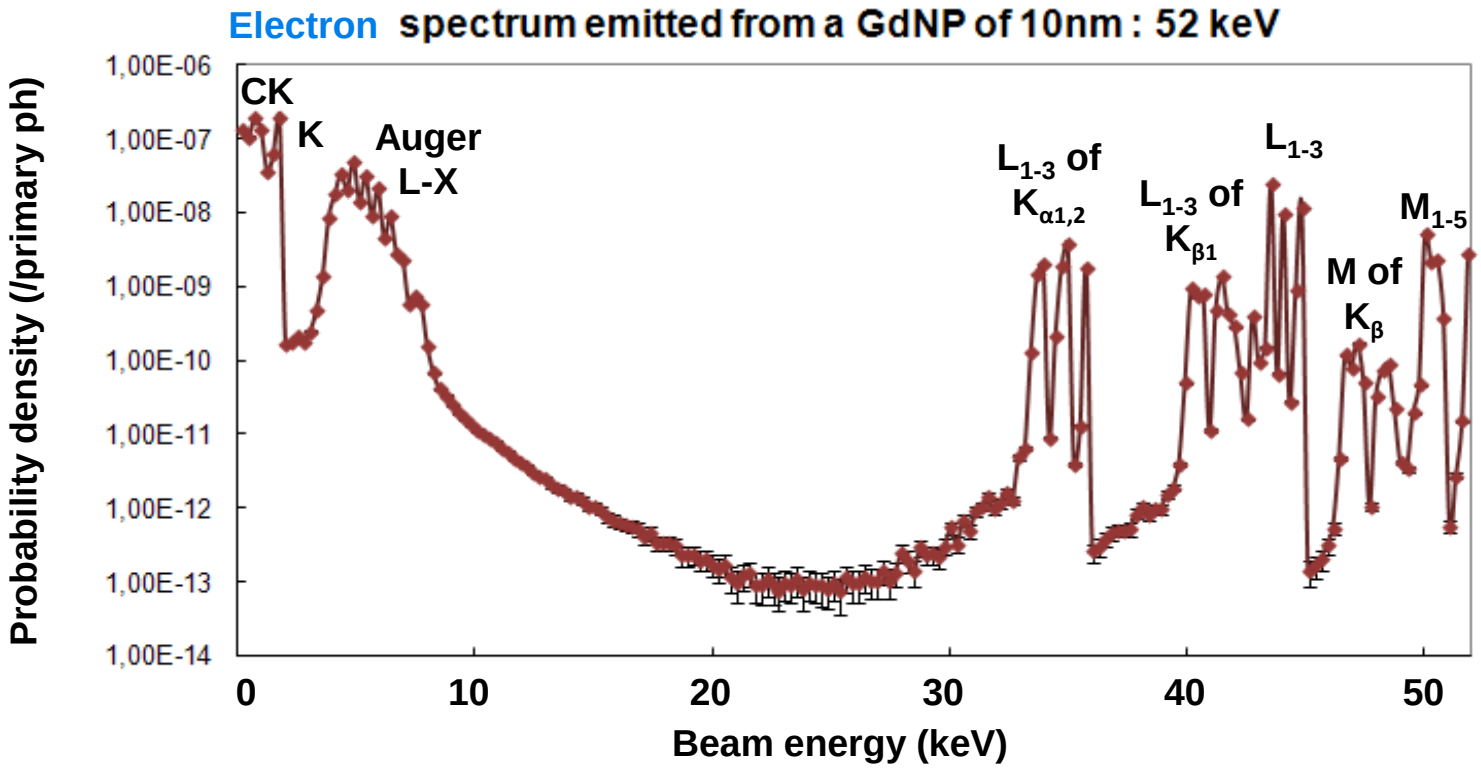
- First study : Dose deposition and spectra of secondary particles emitted from a single AuNP and GdNP.



Photon detector
Electron detector
GdNP / AuNP

Simulation results
Spectra from GdNP

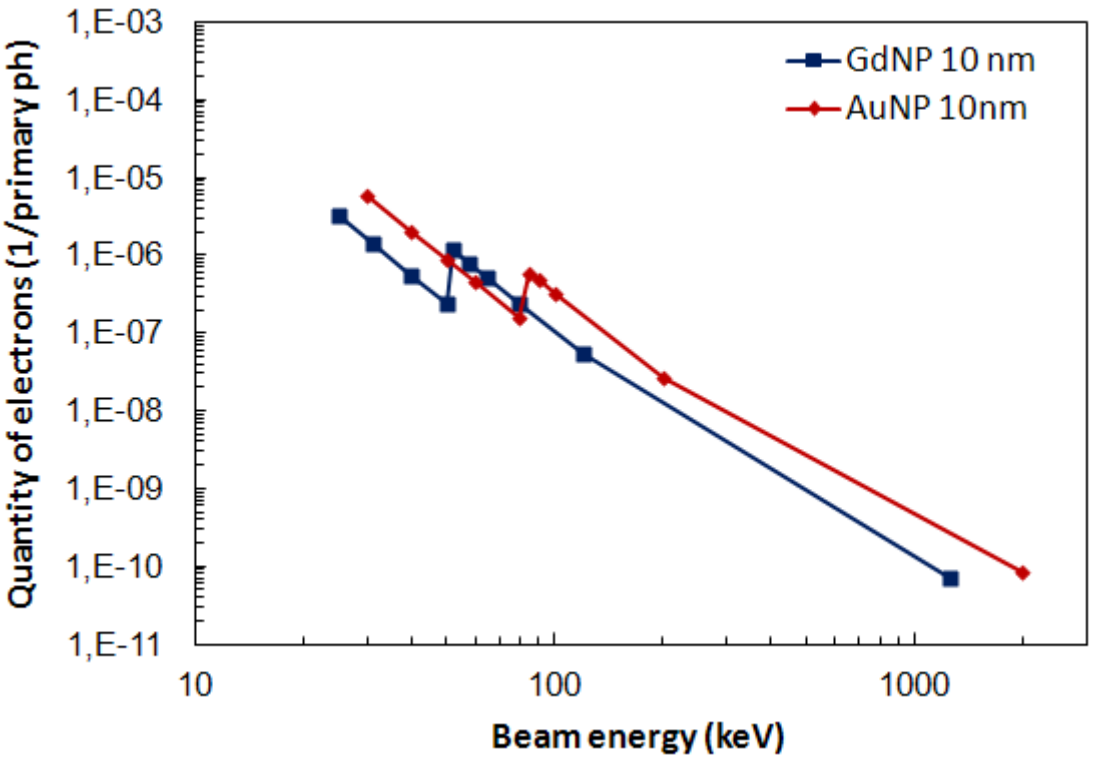


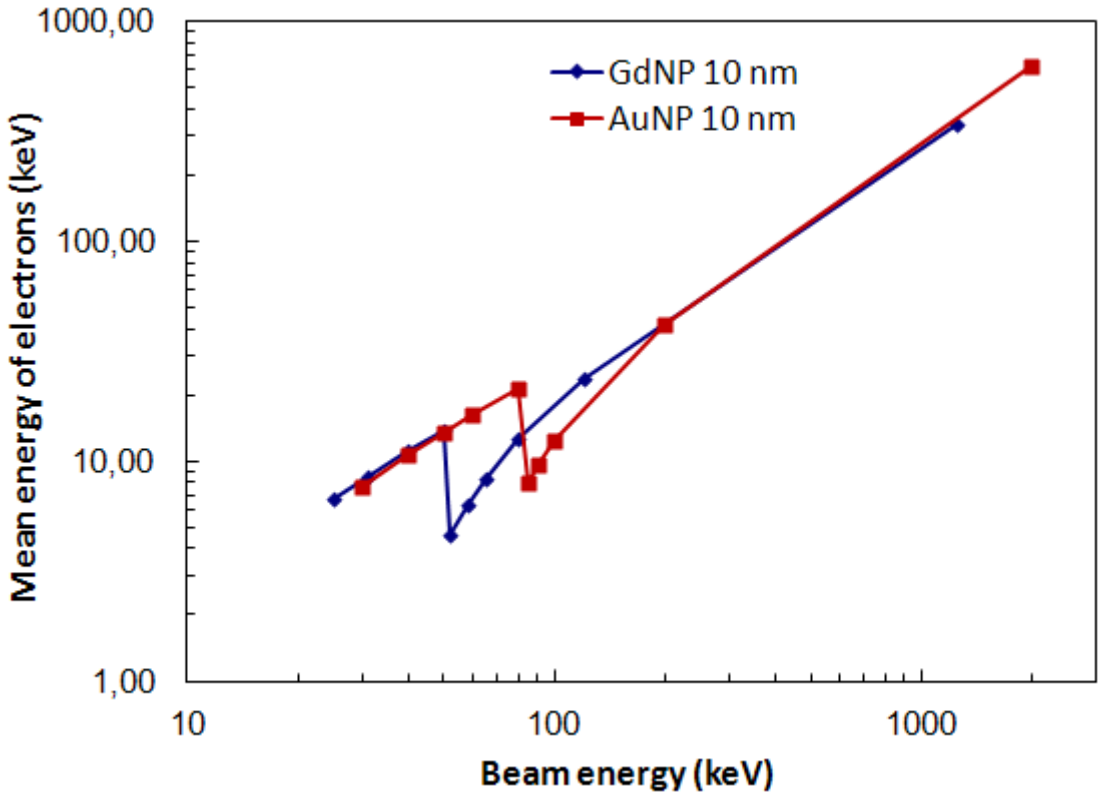


- X-ray beam energy : 52 keV. Diameter of GdNP : 10 nm.
- Gd K-edge : 50.2 keV.
- Au K-edge : 80.7 keV.

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

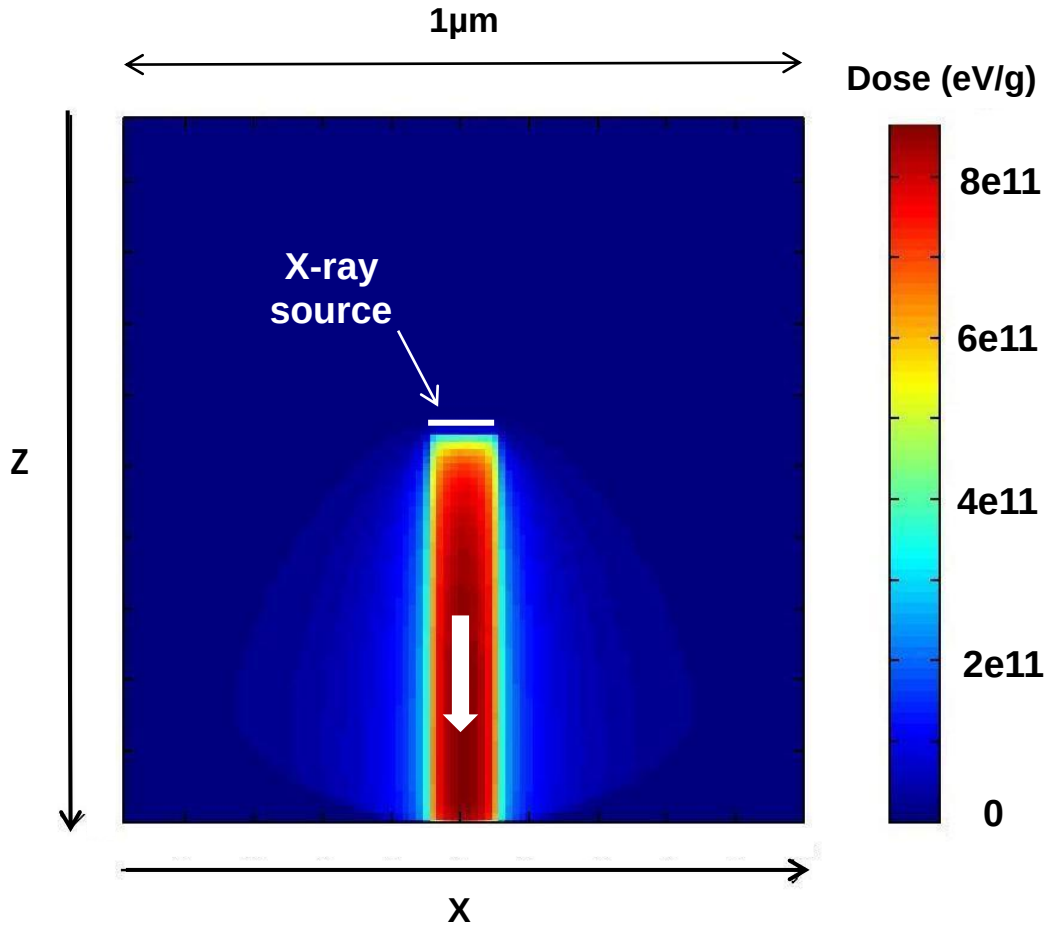
- Electron spectra emitted from a 10 nm diameter AuNP and GdNP as a function of beam energy.
  - Quantity
  - Mean energy

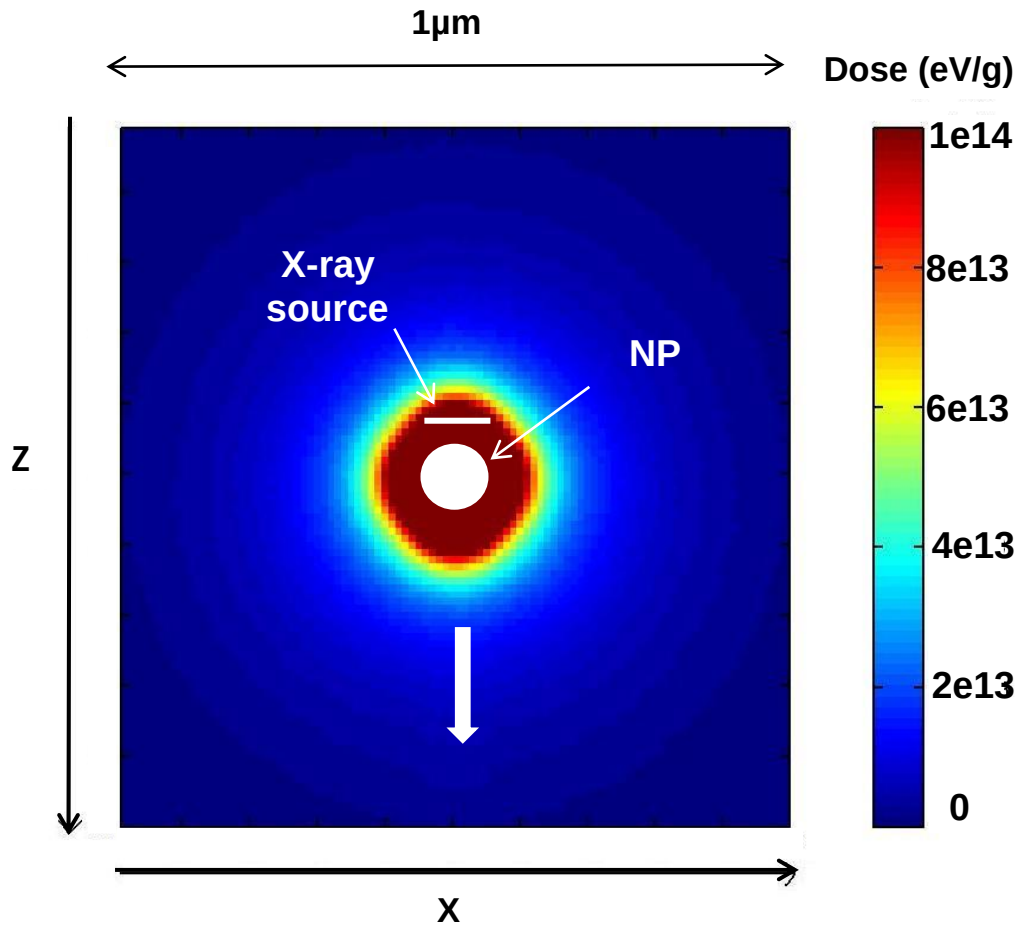




- More electrons produced in Gold except after the sharp Gadolinium K-edge.
- Mean energy lower after the Gd K-edge, provides a more “local” dose deposition.

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

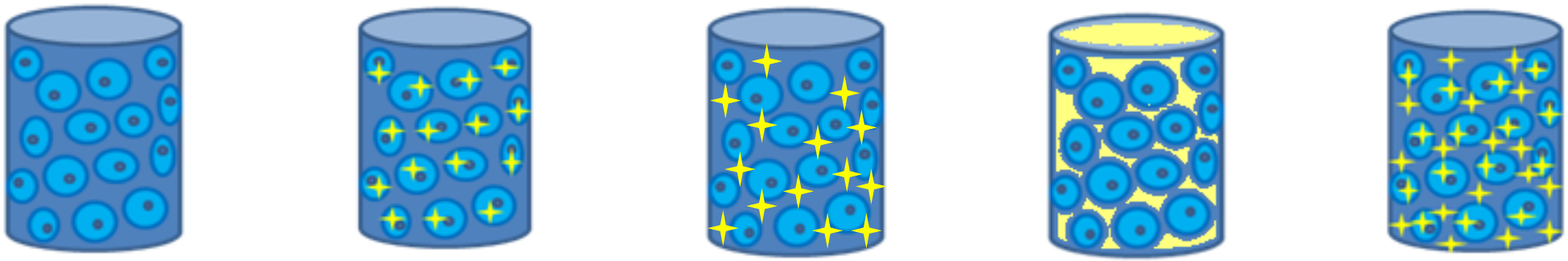




- AuNP : Increase of the dose up to a factor 100 with quasi-isotropic diffusion.

- 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 : 2.1 mg/mL (1.8 mg/mL for the incubated case)

(cf. F. Taupin presentation on Monday (GRC))

- Simulation : Unicellular geometry.

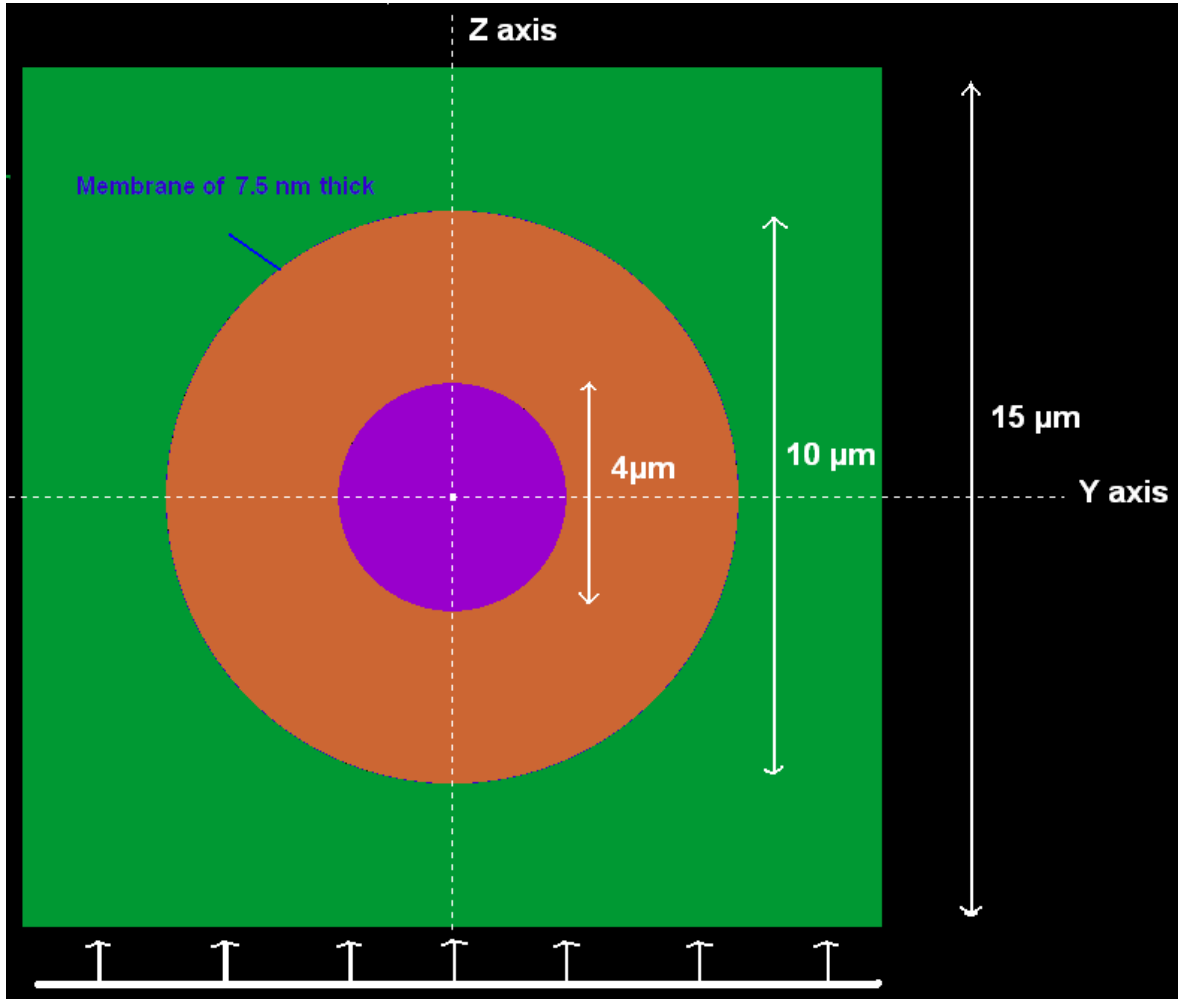
  Nanoparticles substituted with homogeneous water-gadolinium mixture localized into or outside the cell (experimental concentrations).

Nucleus

Cell

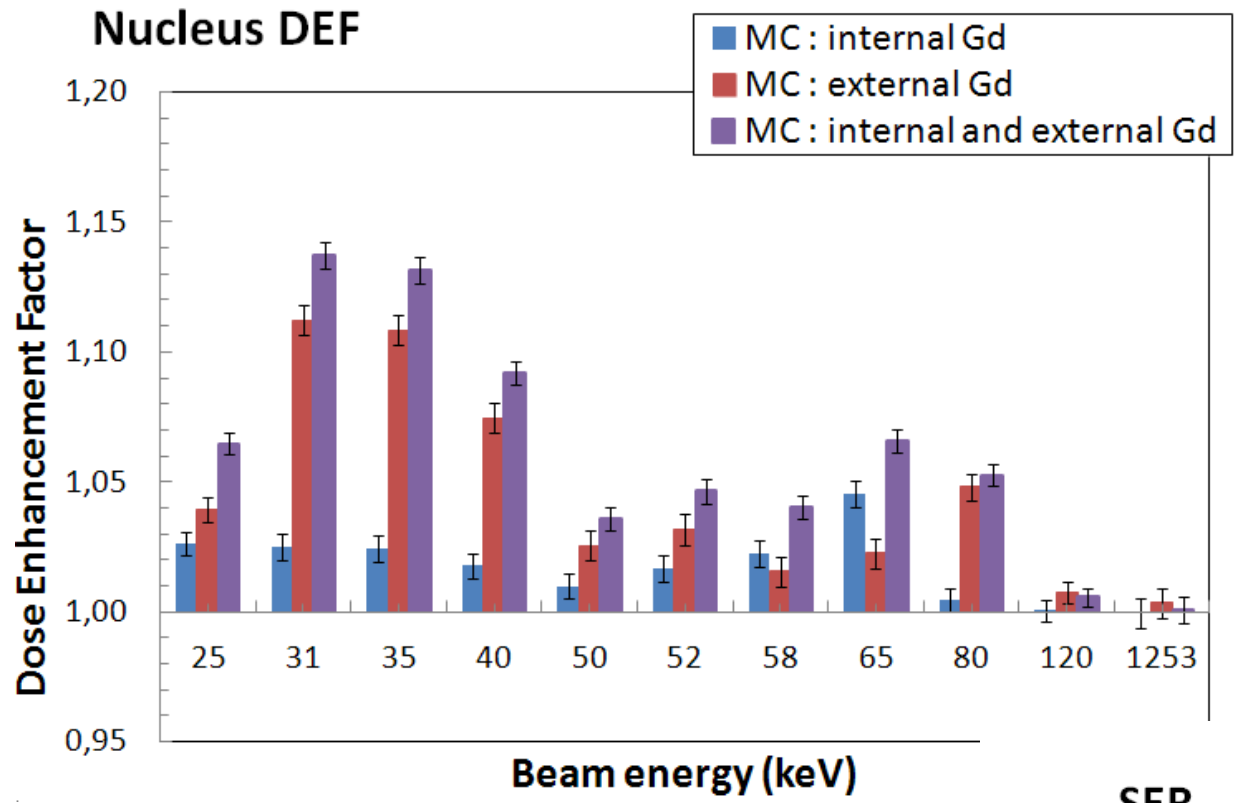
Membrane

Extra-cellular medium



Square monochromatic photon source, 15µm

Experimental comparison
Dose Enhancement Factor

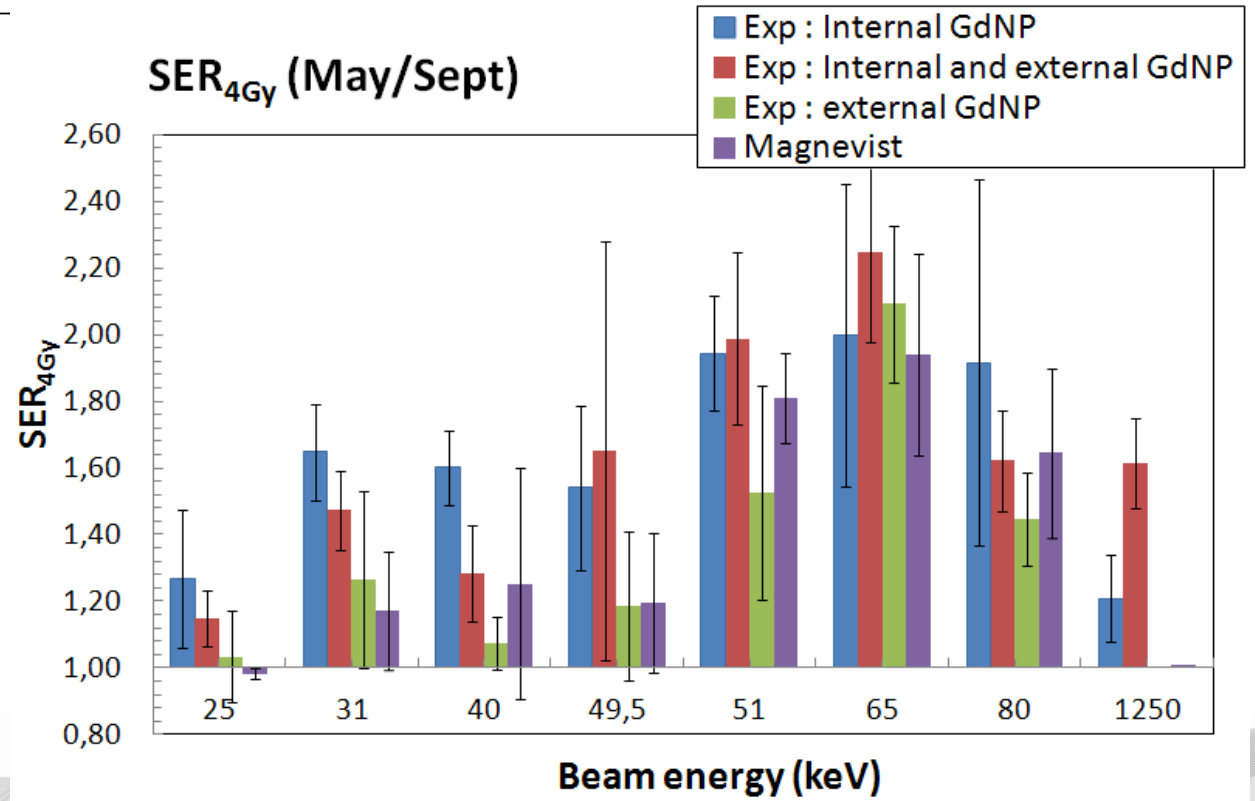


$$DEF = \frac{\text{Dose (Gd)}}{\text{Dose (water)}}$$

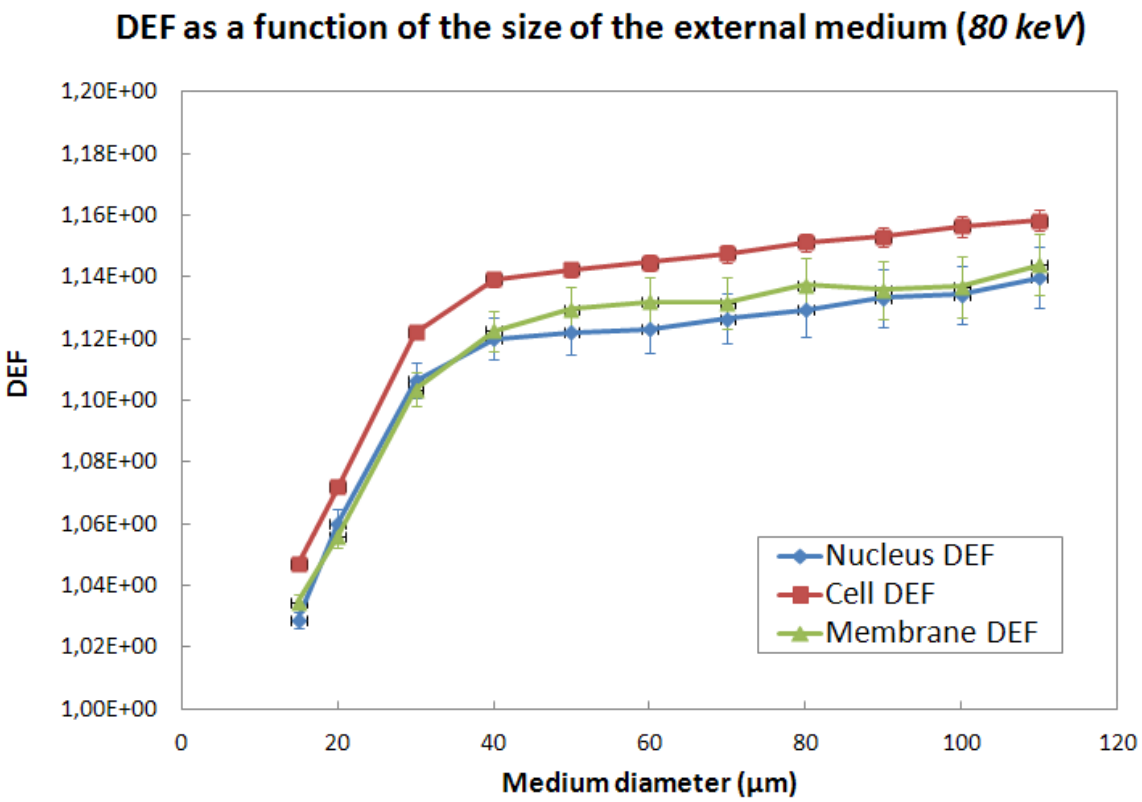
- Maximum DEF obtained of ~1.15 for internal and external Gd.

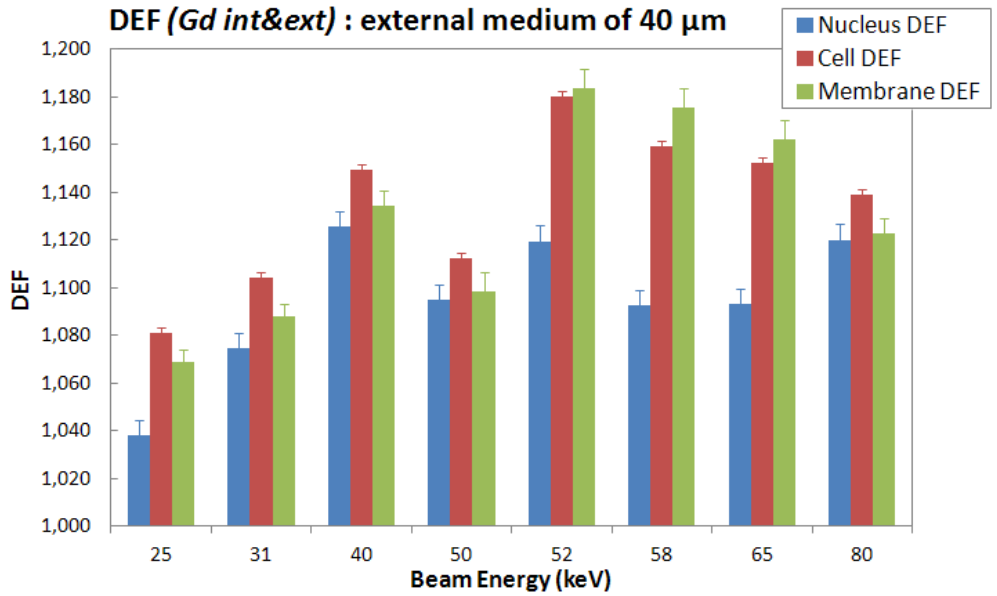
$$SER_{4GY} = \frac{\text{Survival at 4Gy (control)}}{\text{Survival at 4Gy (Gd)}}$$

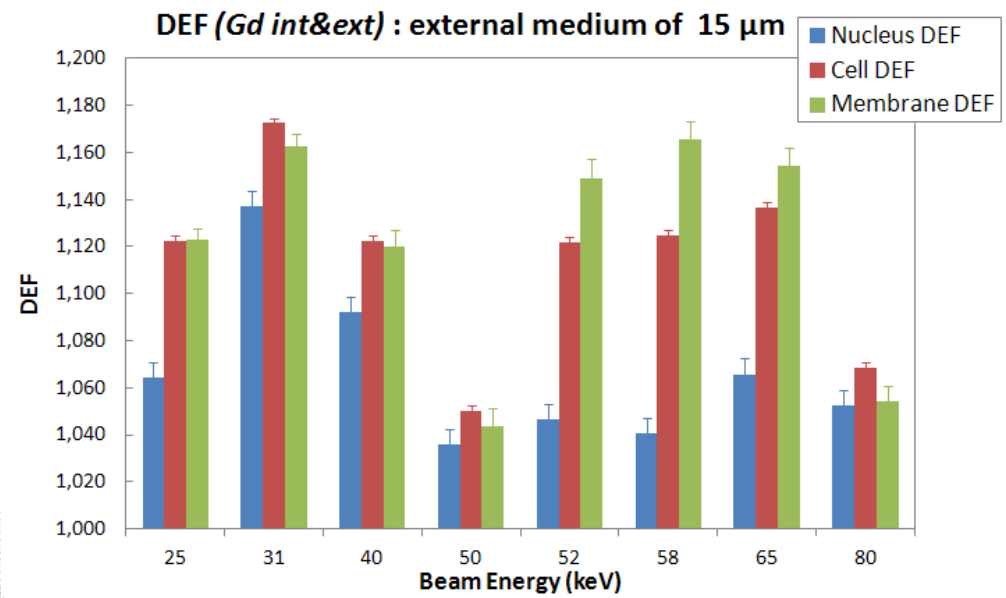
- Experimental SER_{4Gy} much higher (up to 2.25 for 65 keV).



- Size of the extra-cellular medium : 15 to 110 µm. Same size for the X-Ray beam.

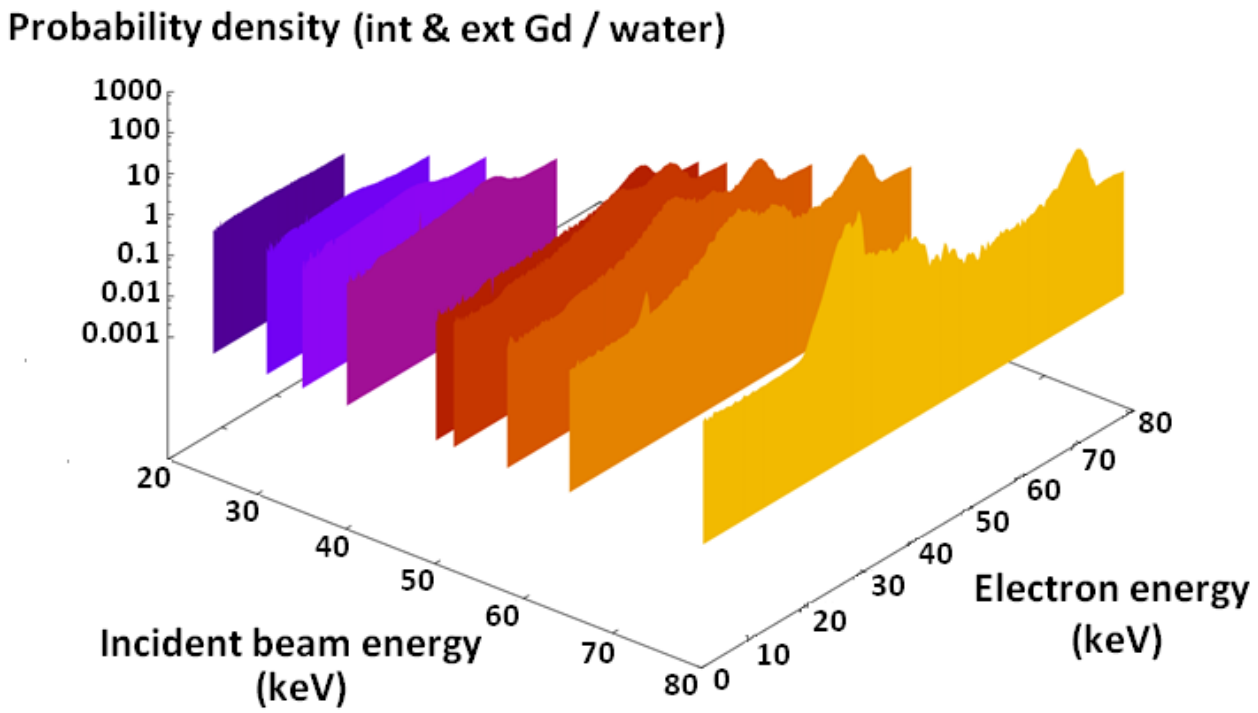






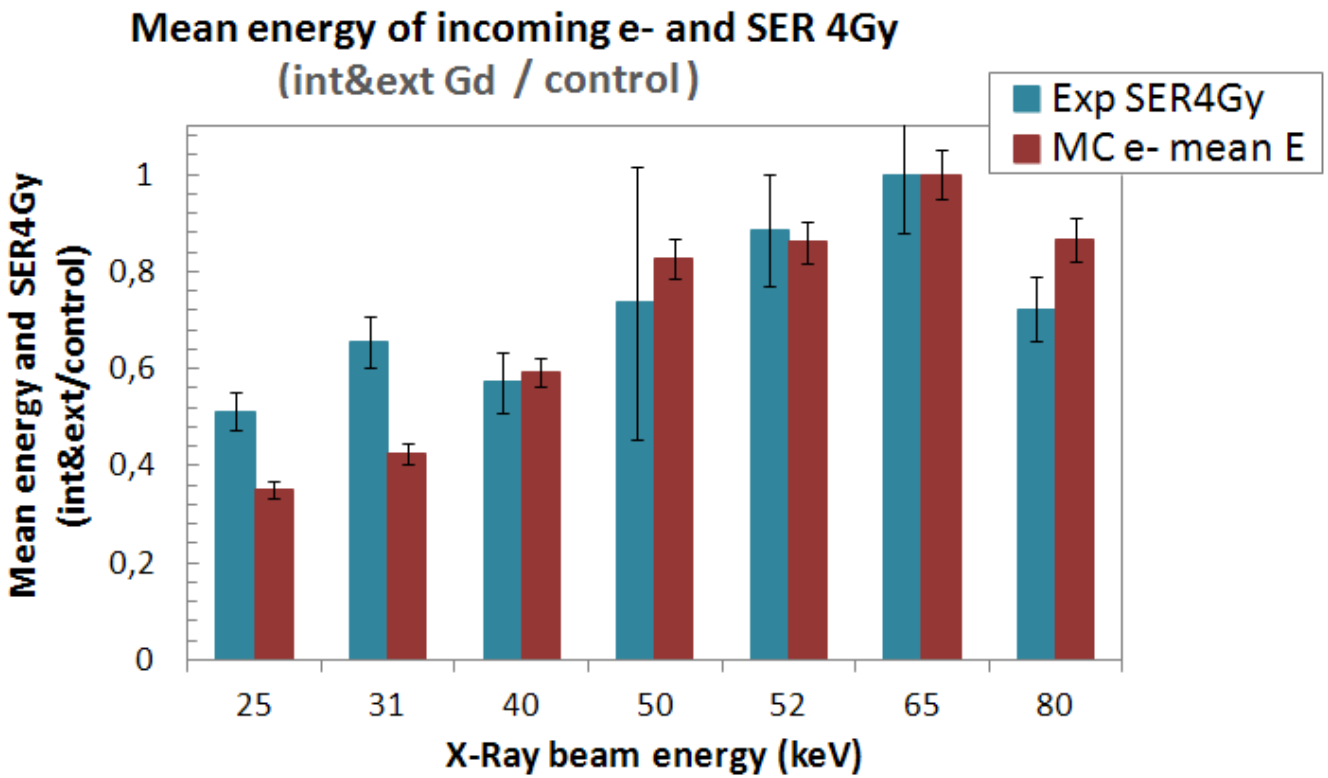
Experimental comparison

Electron spectra incoming on nucleus



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

  (*ex : int&ext Gd / water*)

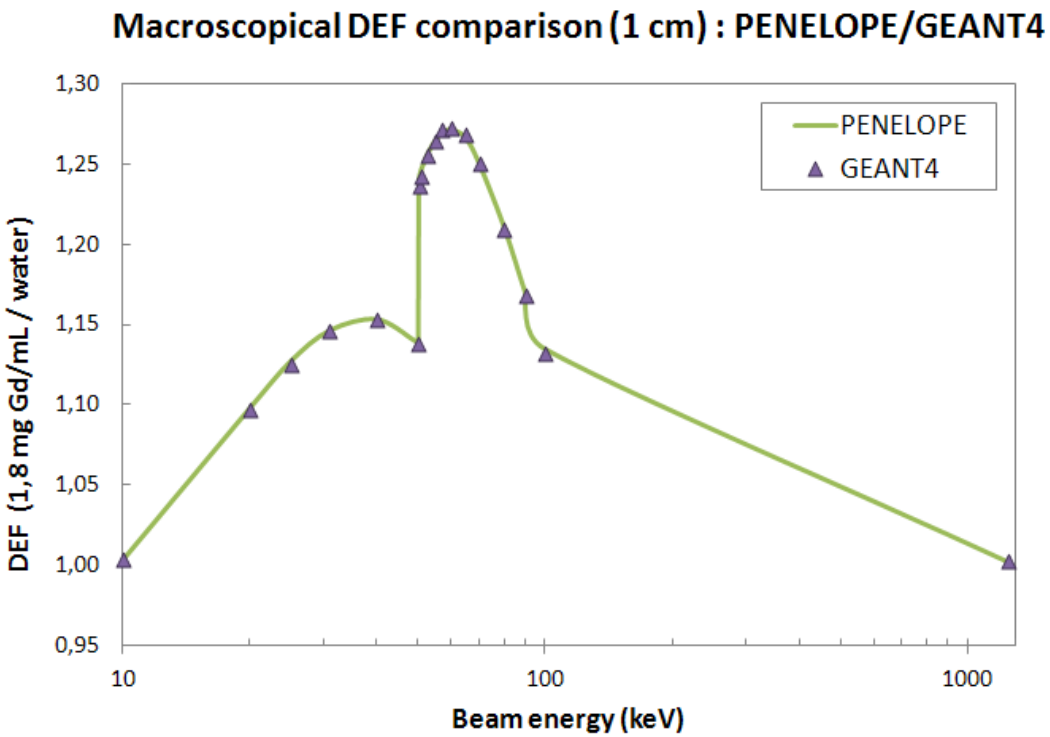


- Experimental comparison normalized at 65 keV :

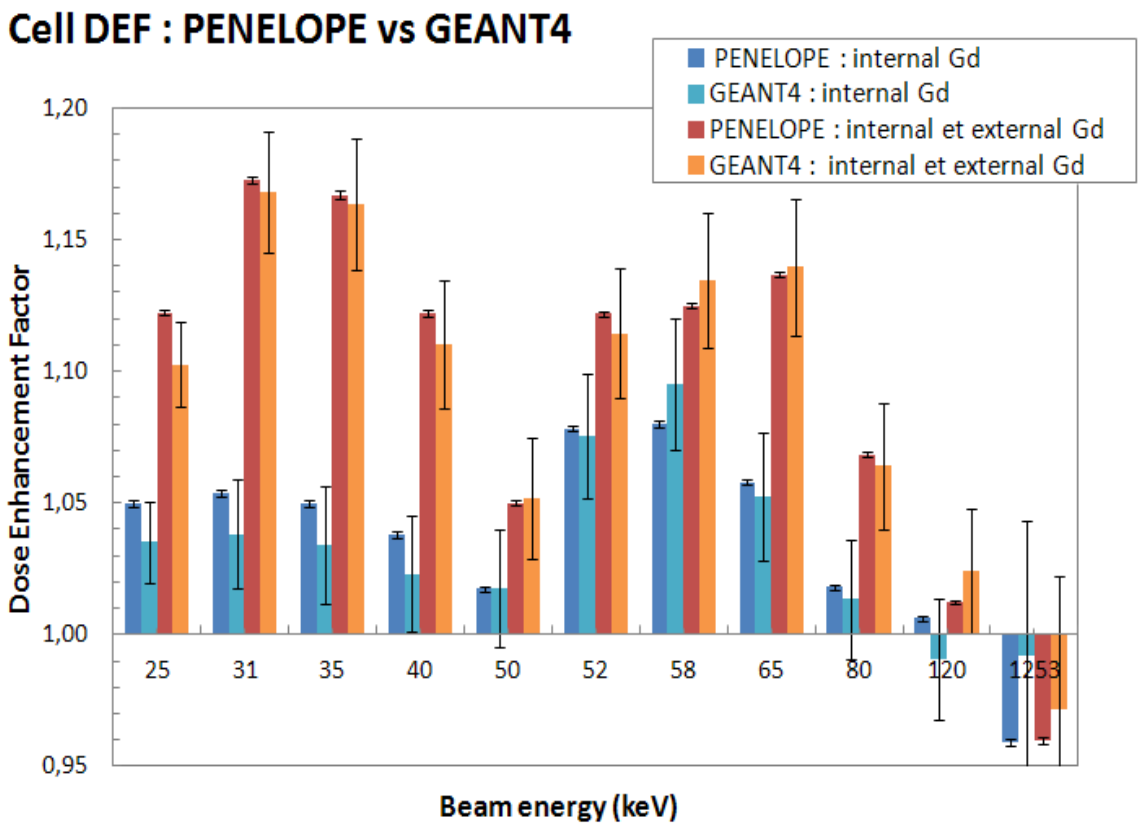
  Good correlation.

- GEANT4 : General purpose Monte Carlo code allowing to transport particles in matter for a wide range of applications (high energy physics, nuclear, space, medical…).
- Electromagnetic physical models for low energy electron and photon transport :
  - Livermore
  - Penelope
  - DNA
- Advantages compared to PENELOPE code :
  - Flexible
  - Complex geometries
  - Access to more detailed track information
- Drawbacks :
  - Lack of variance reductions for small structures.

- Macroscopical DEF : Cube of 1 cm.

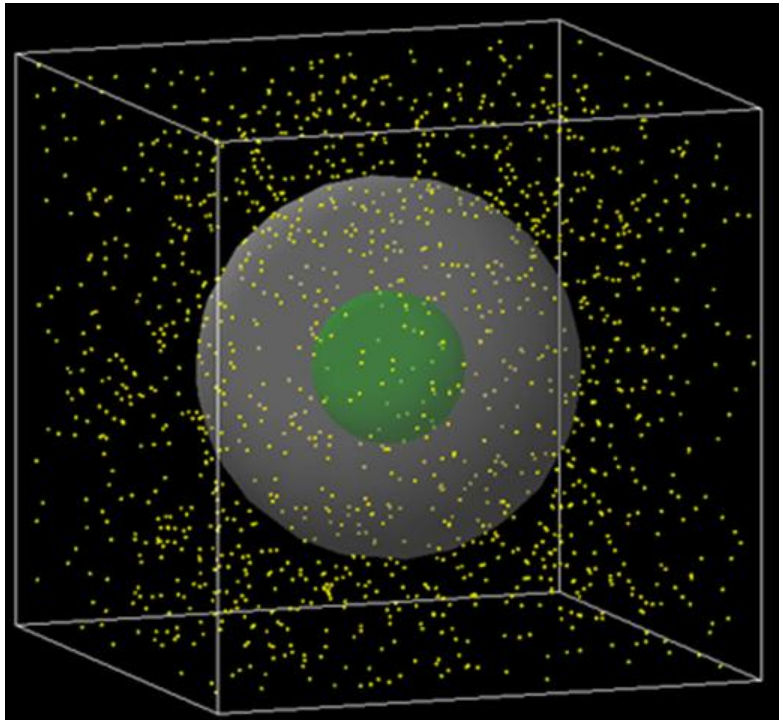


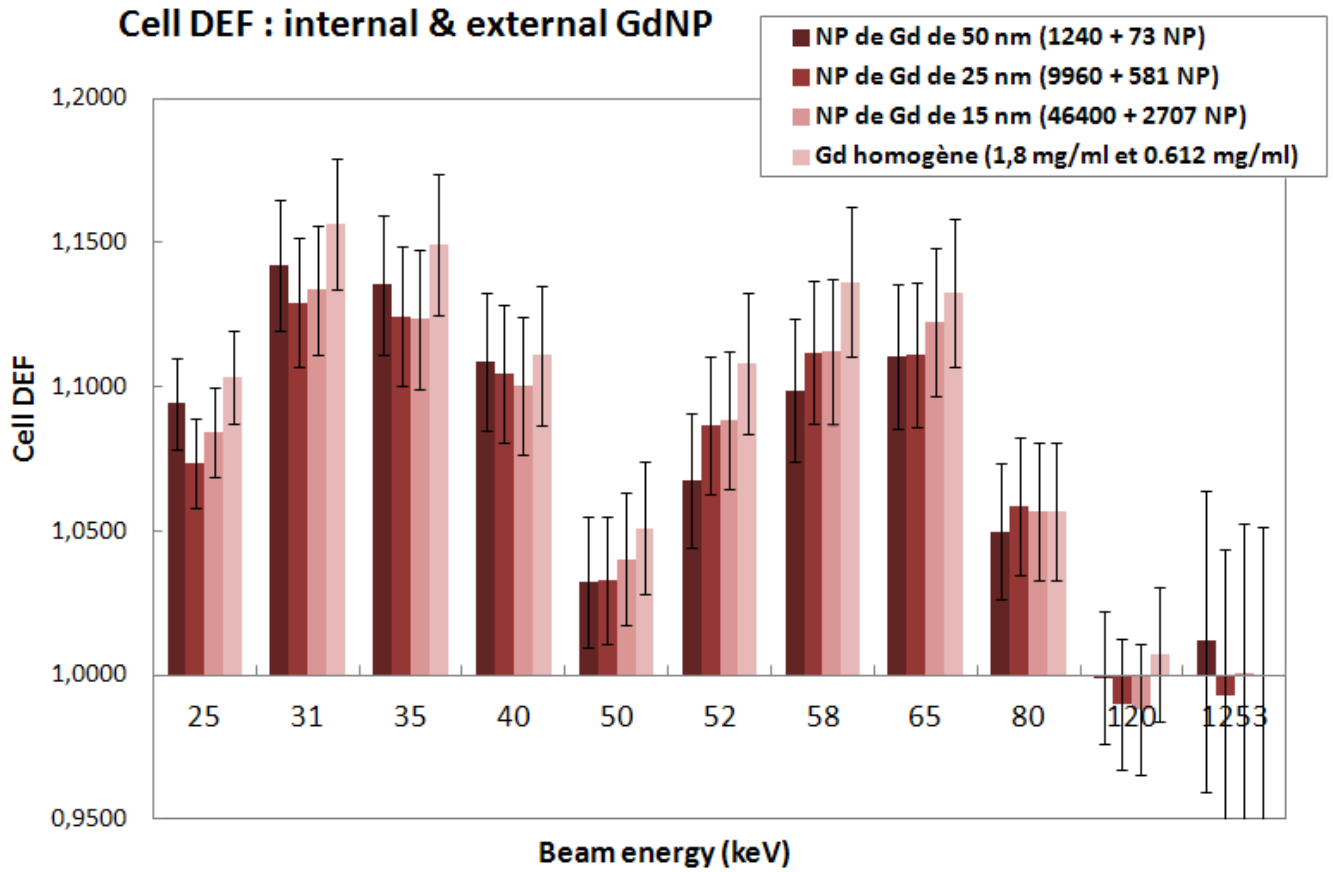
- Microscopical DEF : Cell.



- Coherent results between PENELOPE and GEANT4: problem of statistics for the small volumes (variance reduction).

- Cell geometry : consideration of nanoparticles of different sizes (R = 15 – 50 nm)

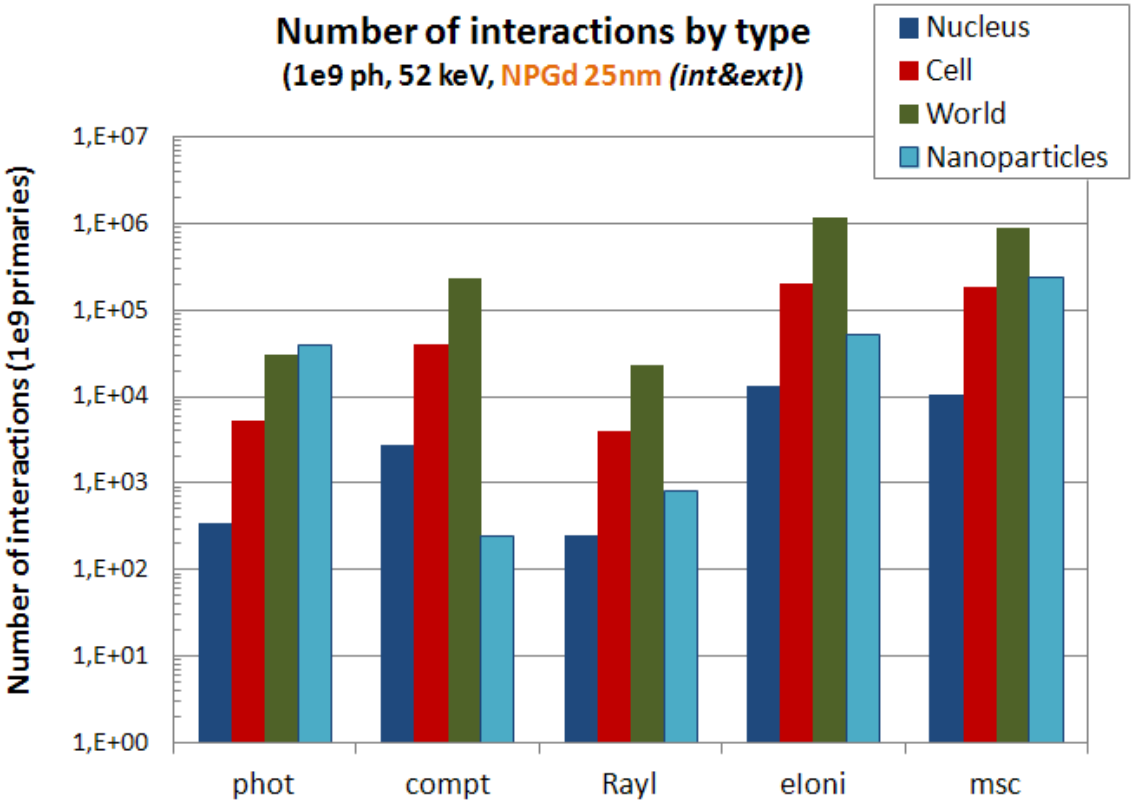


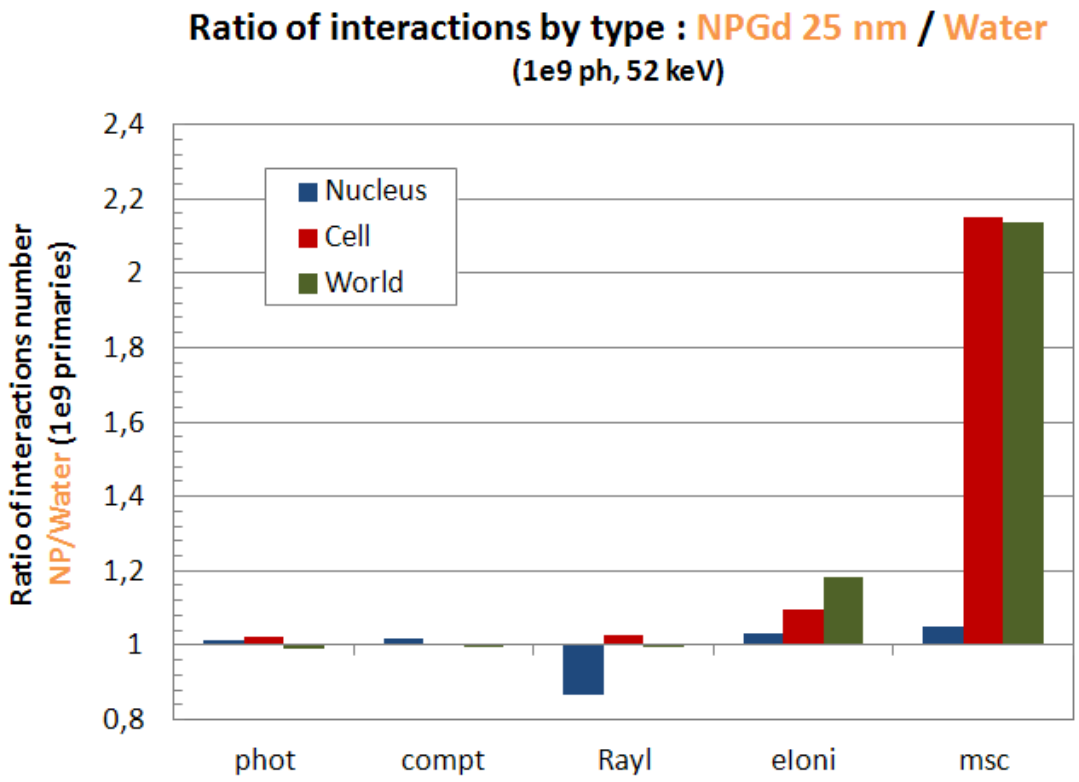


- Coherent results between homogeneous / NP. Auto-absorption of low-energy electrons into the NP.

Code comparison : GEANT4
Number of interactions : 52 keV

- Photon interactions : photoelectric, Compton, Rayleigh
- Electron interactions : Ionization, multiple scattering





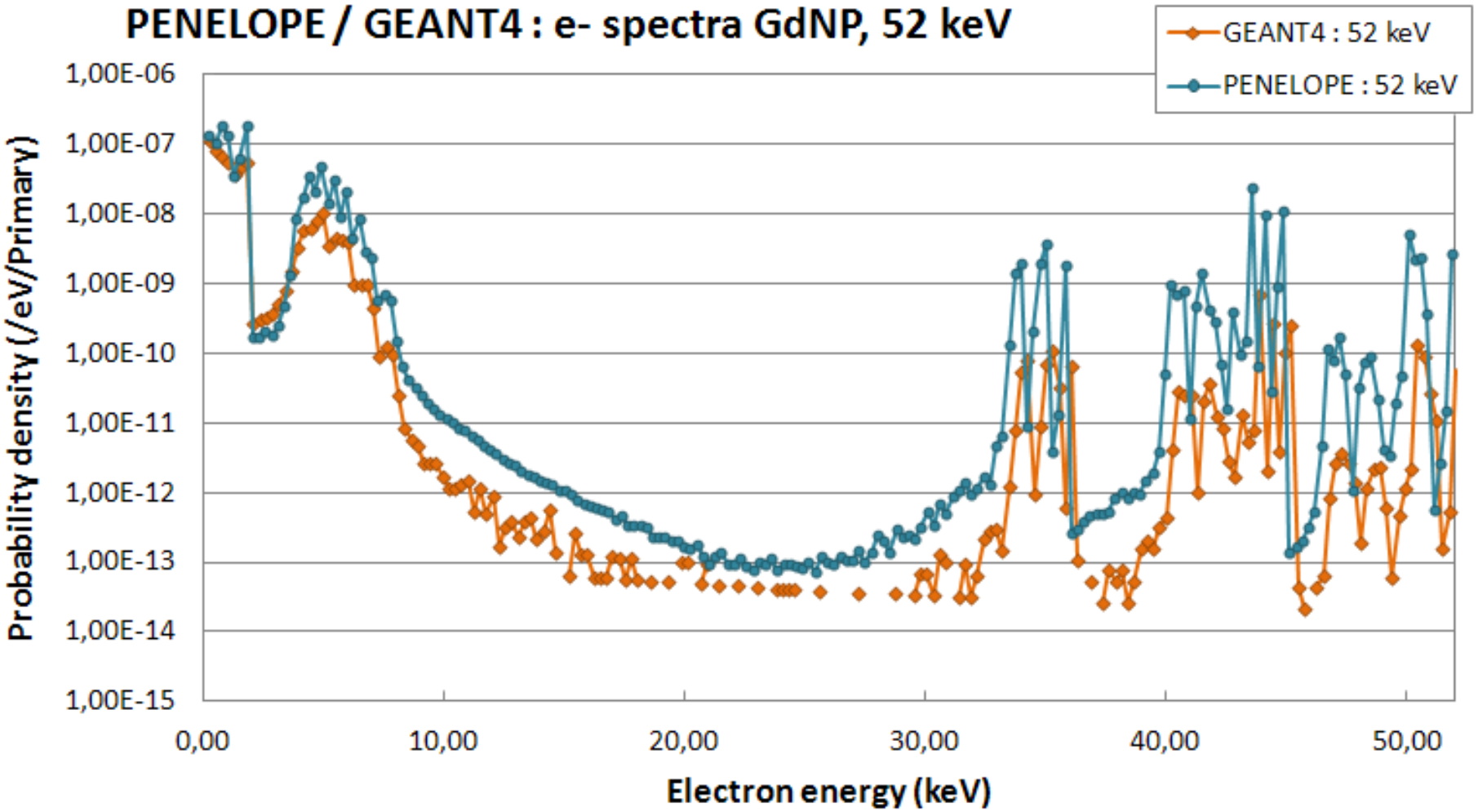
- Conclusions :
  - Nanoparticle model (*PENELOPE*): Study of secondary particles emitted under irradiation for different beam energies and comparison Gd/Au.
  - Unicellular model (*PENELOPE*) : calculation of DEF and electron spectra incoming on the nucleus for different conditions.
  - Comparison with experimental data (*PENELOPE*) : encouraging results.
  - Limitation of PENELOPE modeling large number of nanoparticles : GEANT4.
  - Validation GEANT4 / PENELOPE. Very long simulation time with NP for acceptable statistic.

- Prospects :
  - Improve GEANT4 physical model for nanostructures applications.
  - Investigation of track information.

Thank You for your attention

- LM2S:
  - Bénédicte POUMAREDE, Mathieu AGELOU, Juan-Carlos GARCIA-HERNANDEZ, François TOLA.
- Supervisors :
  - Mathieu AGELOU *(LM2S)*
  - Christophe CHAMPION *(Univ. De Lorraine, Metz)*
  - Hélène ELLEAUME *(INSERM / ESRF)*
- Co-workers:
  - Florence TAUPIN *(INSERM / ESRF)*
  - Mélanie FLAENDERS *(INSERM / ESRF)*
  - Jean-Luc RAVANAT *(LAN, CEA Grenoble)*
  - Sébastien INCERTI *(CENBG, Bordeaux)*

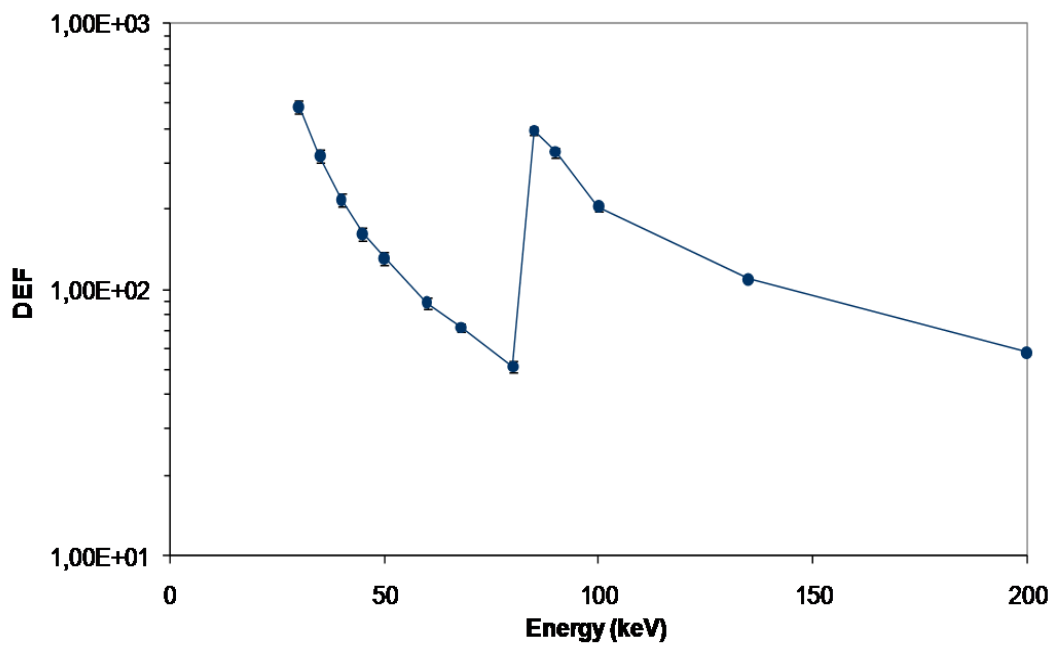
- Comparison of electron spectra between PENELOPE and GEANT4.
  (52 keV, NPGd 10 nm diameter). Good correlation. Lack of statistic for GEANT4.

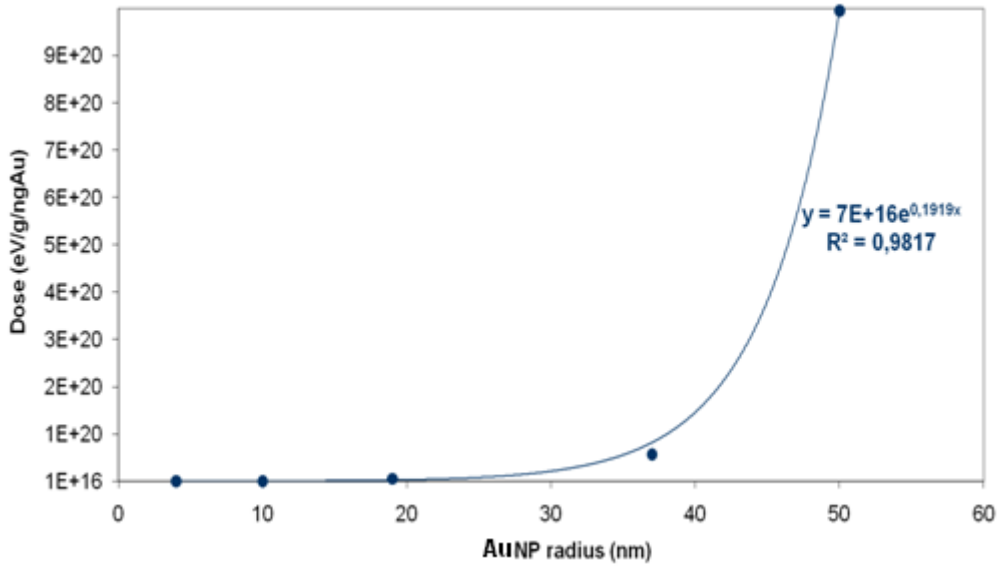


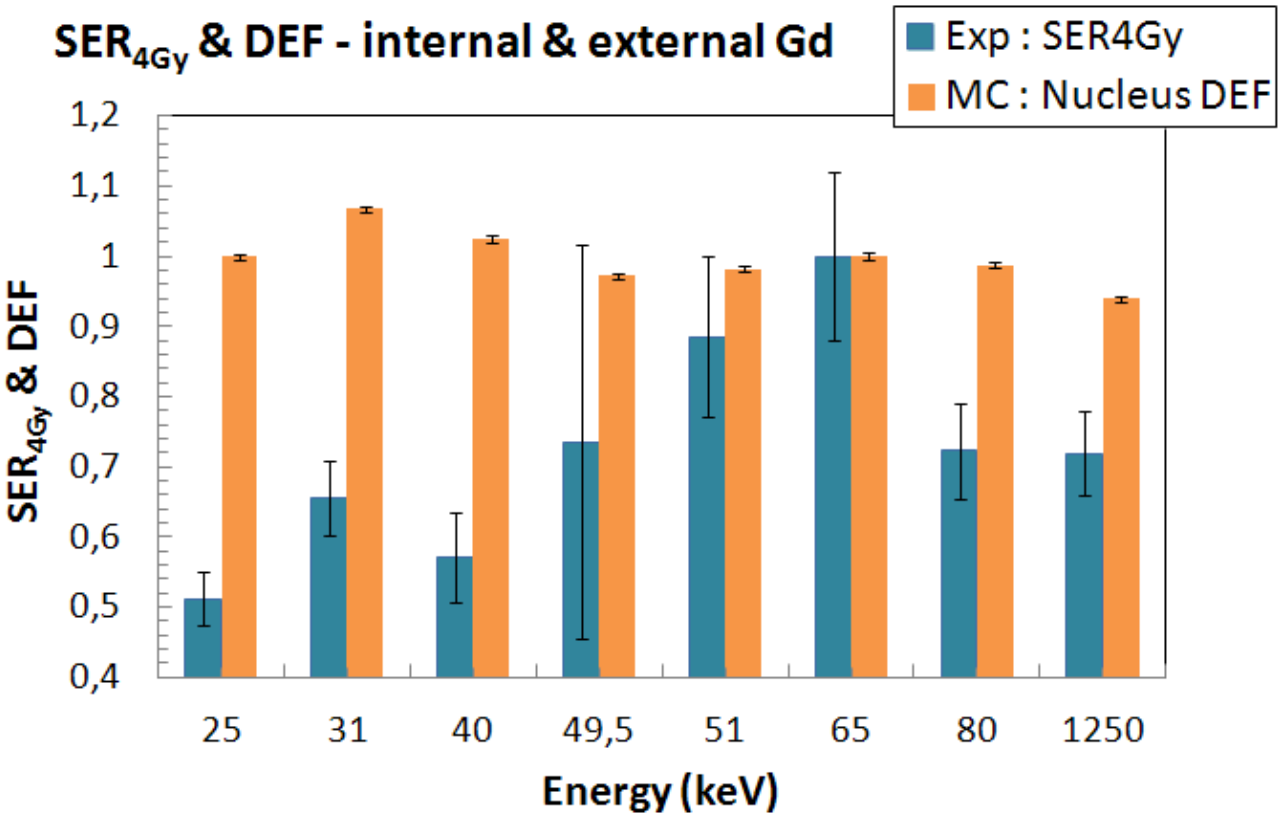
DEF 1µm around 1 NP

- Gd properties :
  K-edge : 50.2 keV, Z : 64, density: 7.9 g/cm^3
- Au properties :
  K-edge : 80.7 keV, Z : 79, density: 19.3 g/cm^3

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







- 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.