Nanoparticles and protontherapy: disentangling possible physical effects

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New approaches in radiotherapy
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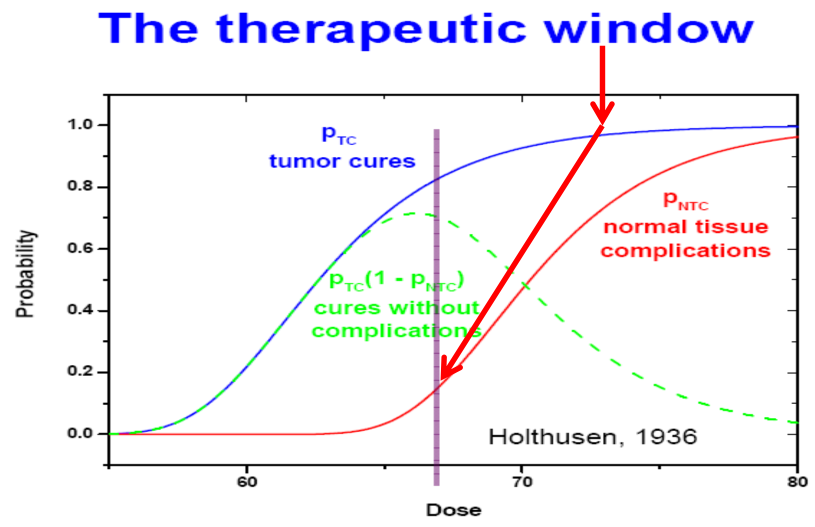
Overview: Nanoparticles (NP) and radiotherapy (RT)

Promising avenue for the improvement of the therapeutic index in RT

-To try to increase the local dose deposition in the tumor

NPs : diameter < 100 nm → they penetrate the cell
High atomic number, ex., Au, Gd, etc.

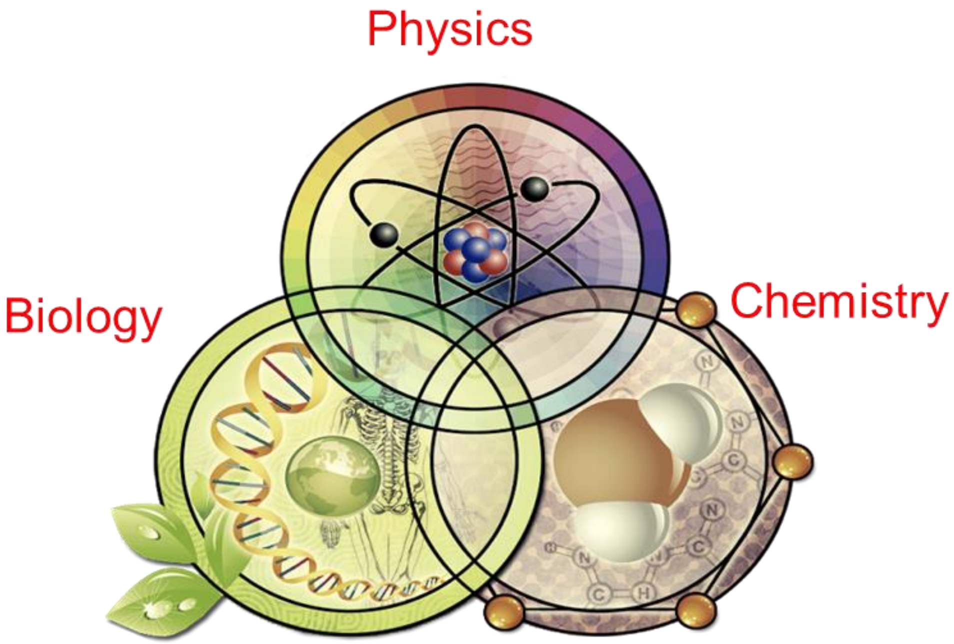


Enhancement of the damage well-proven in RT (x-rays) in numerous biological experiments.

Nanoparticles in radiotherapy

- Radiosensititazer effect difficult to predict. It depends on:
  - ✓Cell line
  - ✓ NP size
  - ✓ Concentration and location of NP inside the cell
  - ✓Beam energy

- **Mechanisms not yet completely clear**



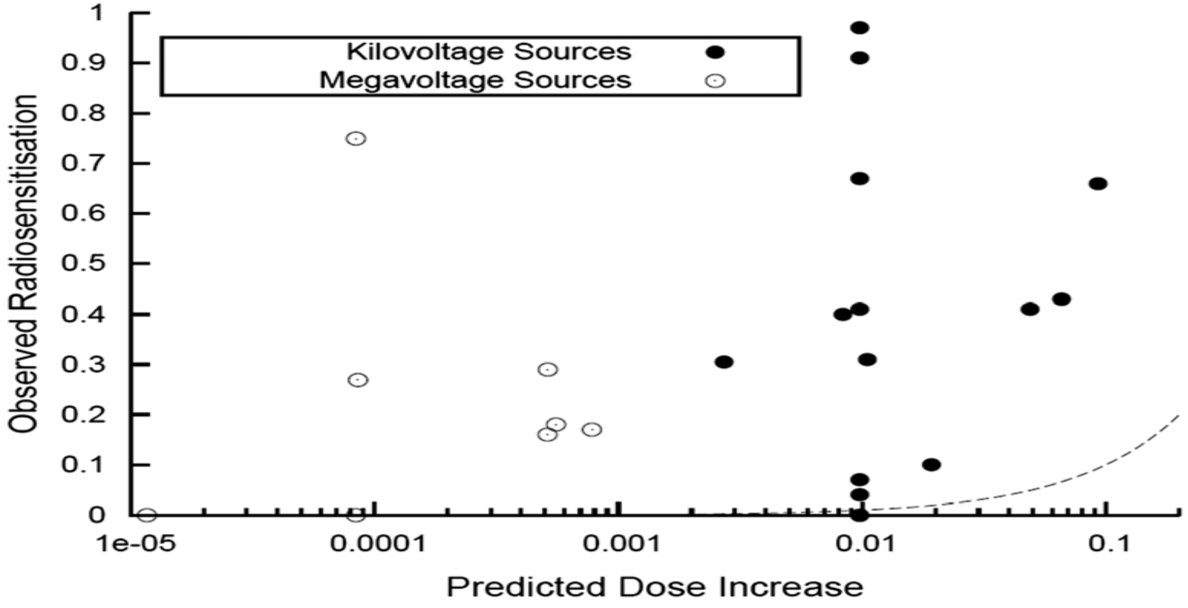
Nanoparticles and x-rays: physical effects?

Low E photons + high Z elements = preponderance of photoelectric effect

→ photo-electrons→ short range

→ atomic deexcitation→ Auger electron cascade with nm range

“cluster” damage → important biological effect of Auger e-



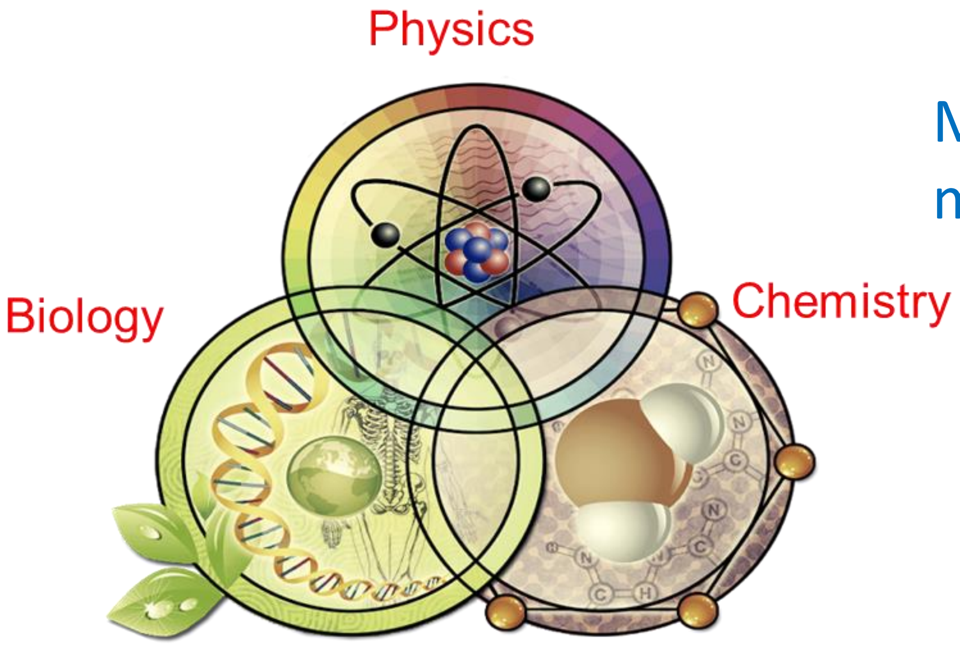
However, incoherence between the predicted values and the results observed experimentally

No apparent correlation

Butterworth et al. Nanoescale (2012)

(Posible) role of enhancement of local dose?

Changes in cellular function?



Molecular modifications?

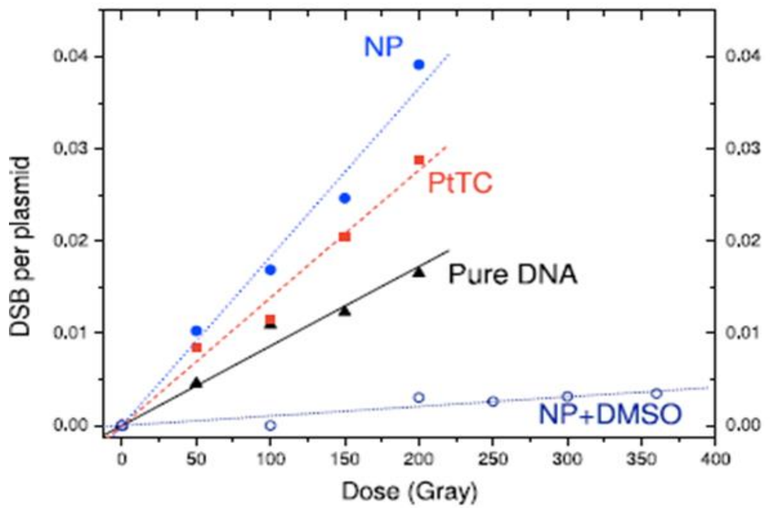
Nanoparticles and hadrontherapy

Porcel et al., Nanotechnol. 2010

Plasmid ADN

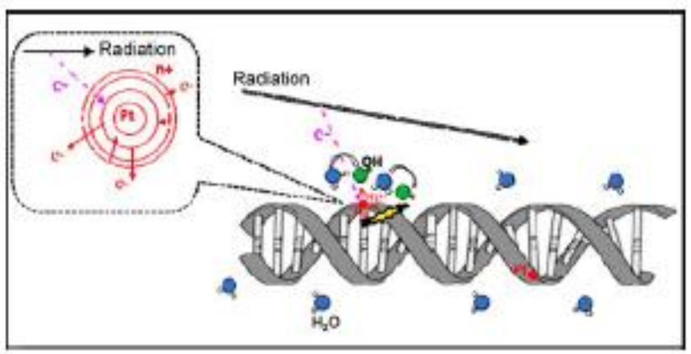
Pt NPs + carbon irradiation

The presence of nanoparticles increase the number of DNA double strand breaks in a factor 2



Efect tentatively assigned to the increase of ionisations (by primary ions and the secondary e-)

- Auger cascades
- Dense production of radical species OH around NP



Nanoparticles and hadrontherapy

- Kim et al PMB 2012

CT6 bearing mice

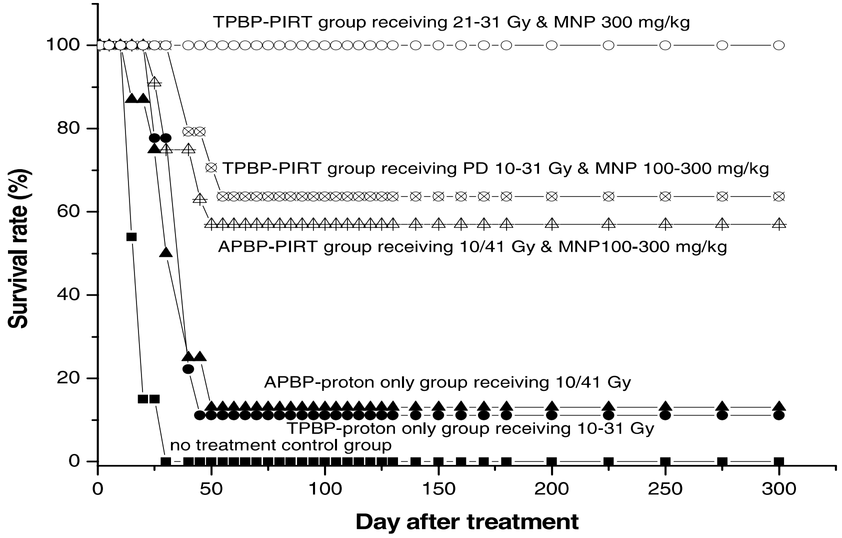
AuNP and FeNP (100-300 mg/kg)

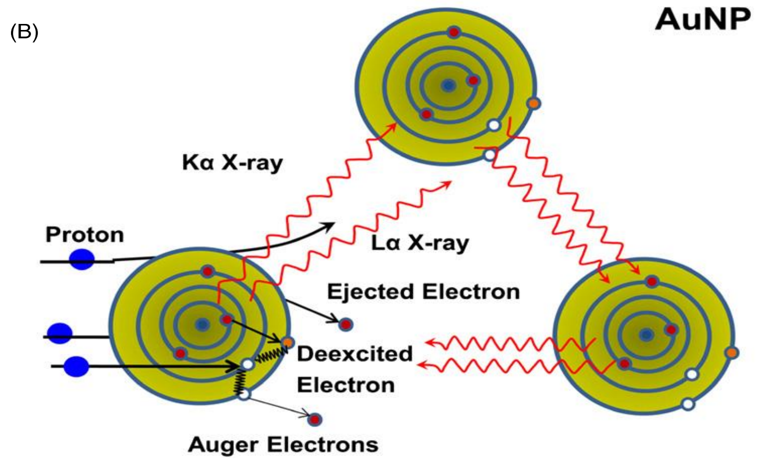
40 MeV proton irradiation

Increase of 50-100% of lifespan in presence of NP

They propose PIXE (particle induced x-ray emission)

Controversial interpretation

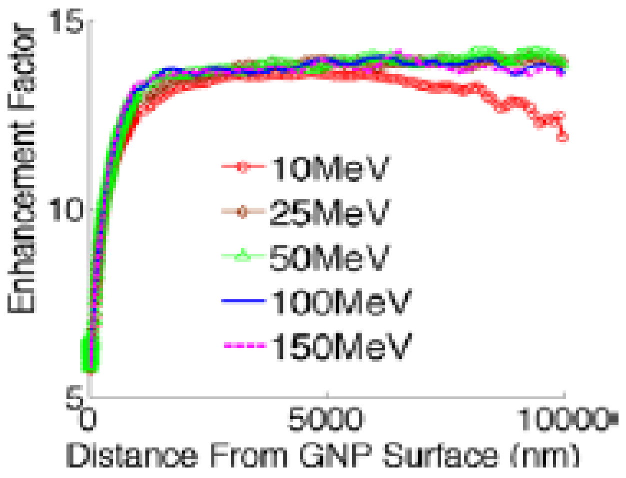


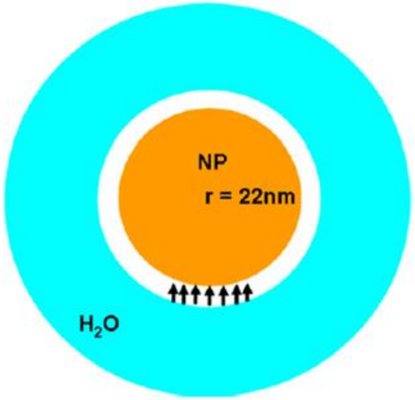


Nanoparticles and protontherapy: Monte Carlo studies

Y. Lin et al PMB 2014

Geant4
Predict increase of local dose of 10

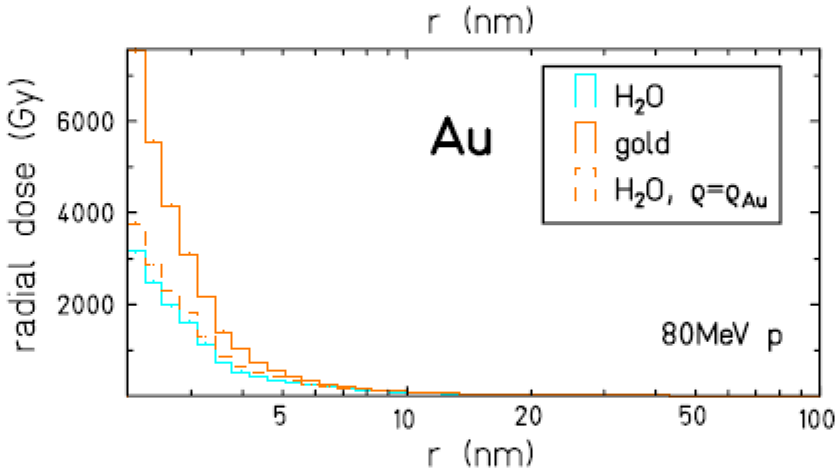


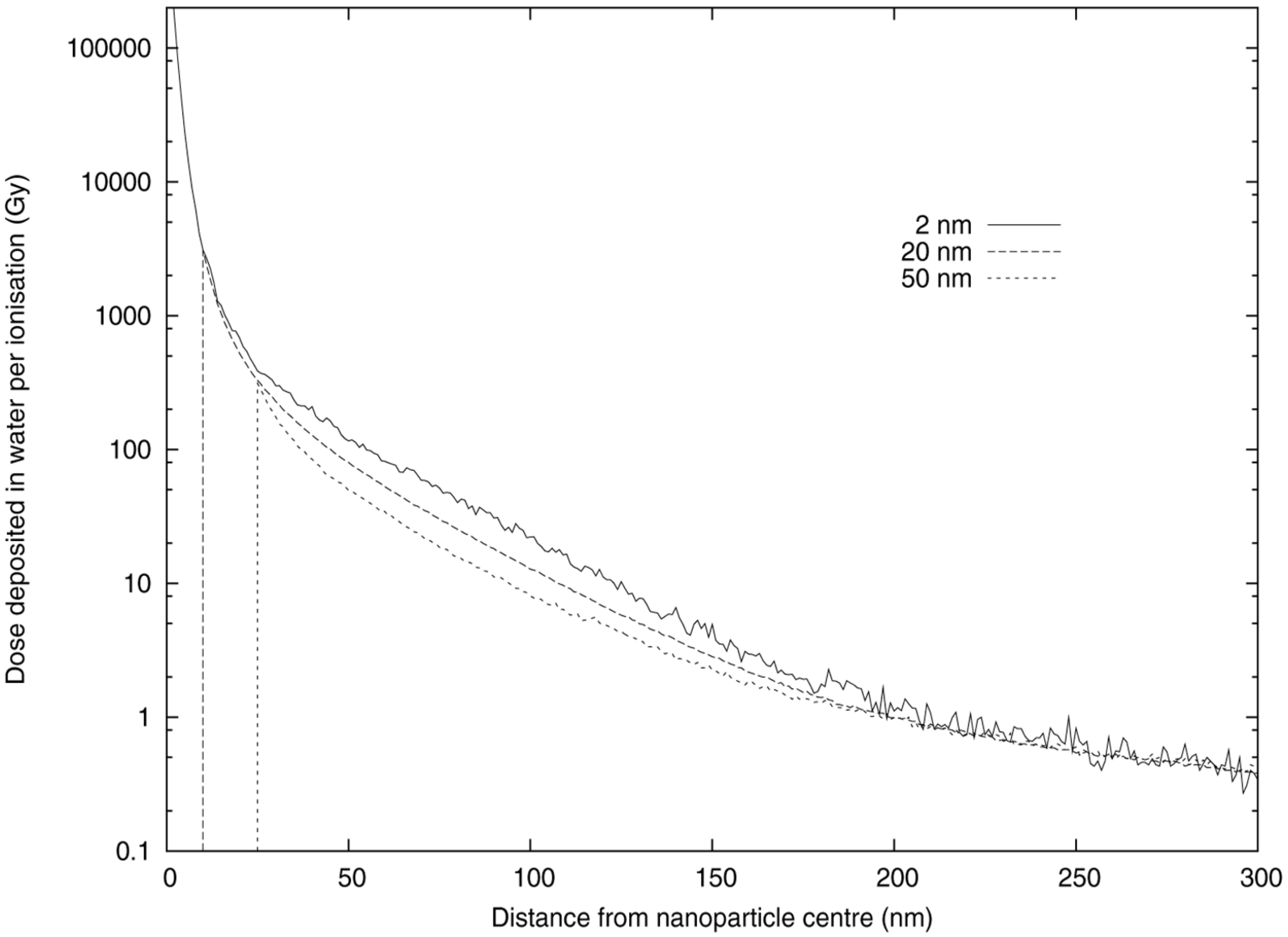


Protons impinging directly into NP

Waltzein et al. PMB 2014

TRAX (Improved cross sections < 100 eV)
Increase of local dose factor 2



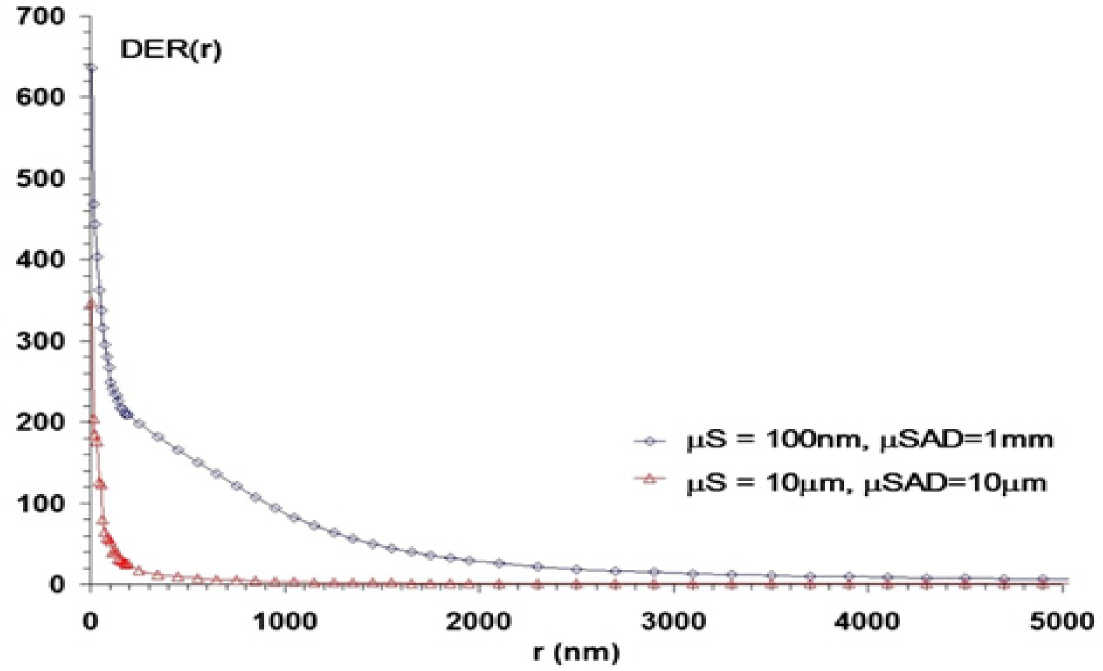


A factor 10000 for low energy x-rays!

McMahon et al 2011

Nanoparticles and protontherapy

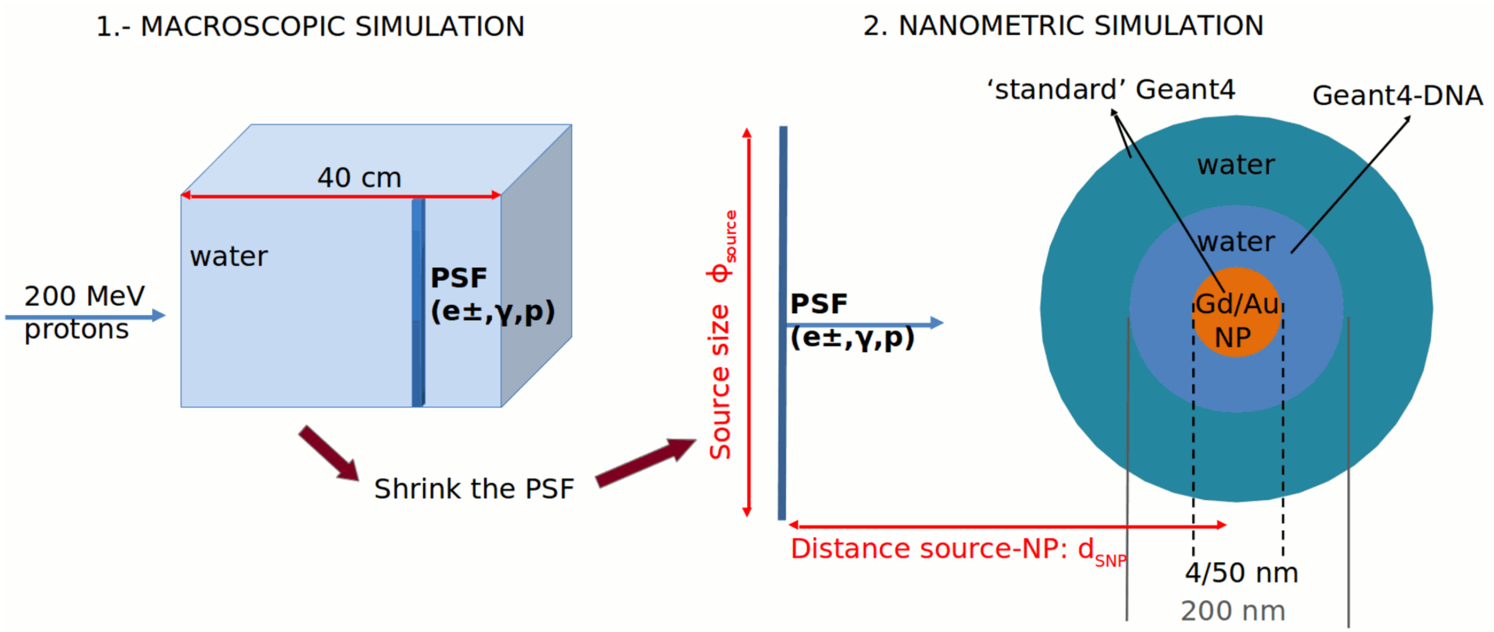
P. Zygmanski et al PMB 2013 "Dependence of Monte Carlo microdosimetric computations on the simulation geometry of gold nanoparticles"



The use of small field sizes and short distance source-NPS may lead to irrealistic dose enhancement

Nanoparticles and protontherapy

I. Martinez-Rovira and Y. Prezado, submitted to Med. Phys.



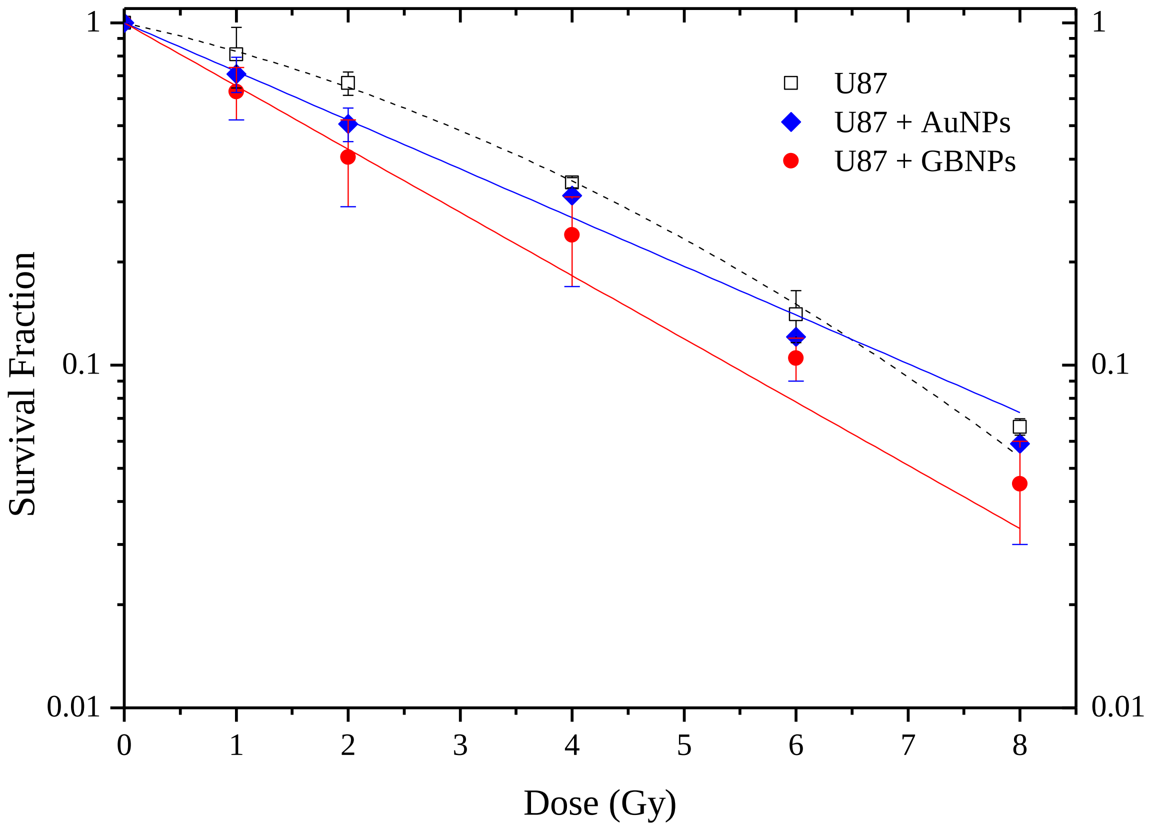
200 MeV protons
AuNP and GdNP

Electron production

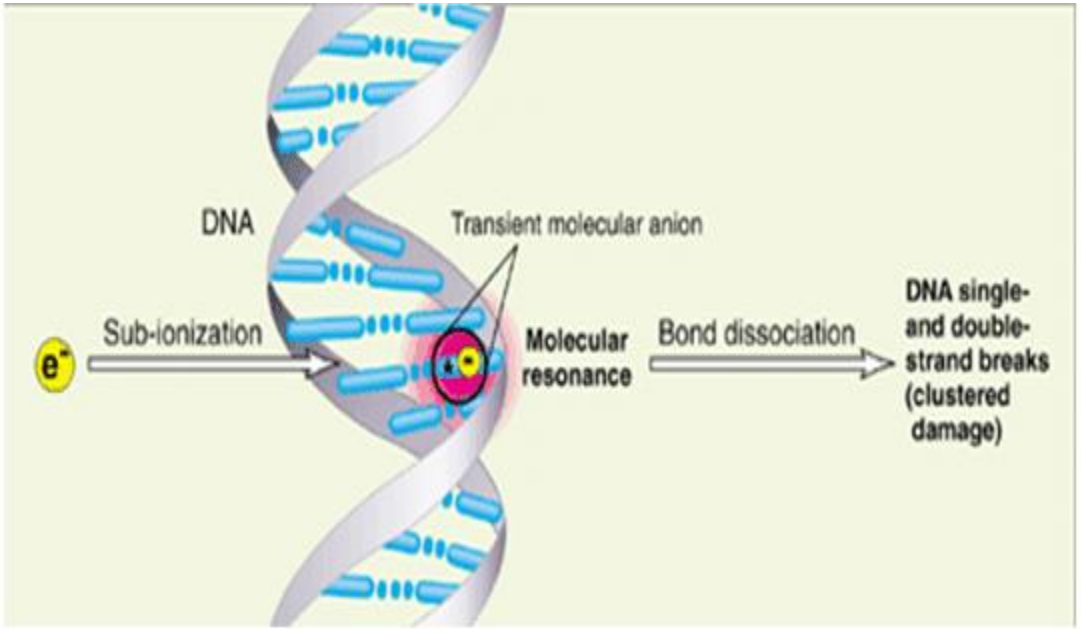
	PHOTON		PROTON	
Concentration AuNp (mg/mL)	0,2	10	0,2	10
Secondary electrons (%)	0,40%	28,30%	0,00%	0,55%
Augers Electrons (%)	32.5%	1357%	0,00%	33%

E< 100 eV

In vitro experiments NPs + proton irradiation



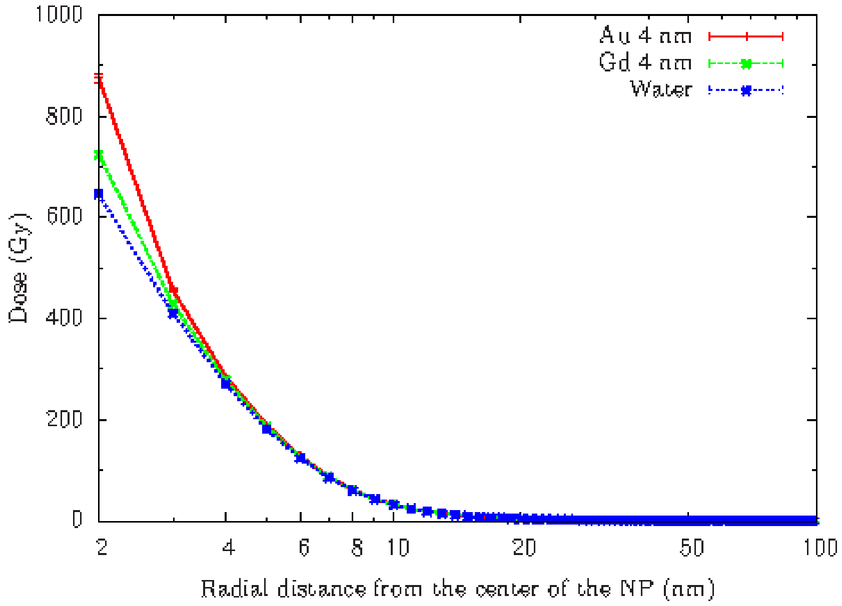
Dissociative electron attachment processes: electrons interact with the molecular constituents of the cell, creating a bond breakage and allowing radicals to interact with other cell components.



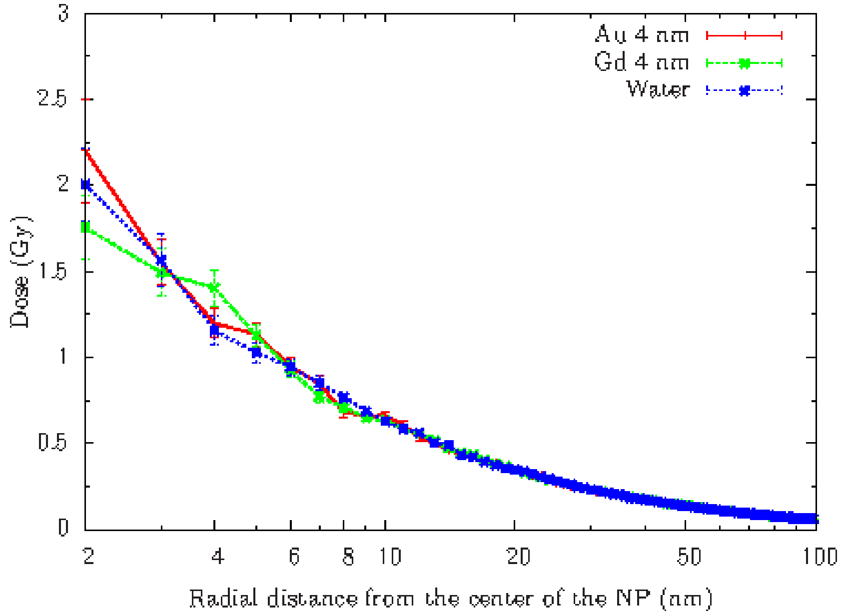
DEA evaluated by using the code Geant4-DNA, which employs cross sections for water only. No significant differences!

Nanoparticles and protontherapy

Protons colliding with NP



Source at d=100 nm from NP



More realistic simulation configurations → reduction of local dose enhancement

The physical effects seem not to play a major role in the radiosensitization observed in biological studies

Conclusions

- No significant contribution of secondary electrons in the combination of protontherapy and NPs as hypothezised

- The energy deposited around the NP show an important (x1000) increase of local energy deposited in the first nm from the NP when irradiated with photons but not with protons

Physical effects seem not to play a major role in protontherapy + NPs

Thank you for your attention

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