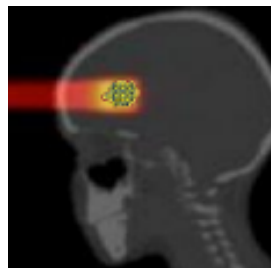


Nanoparticles in proton and ion therapy



Erika PORCEL, Sandrine Lacombe

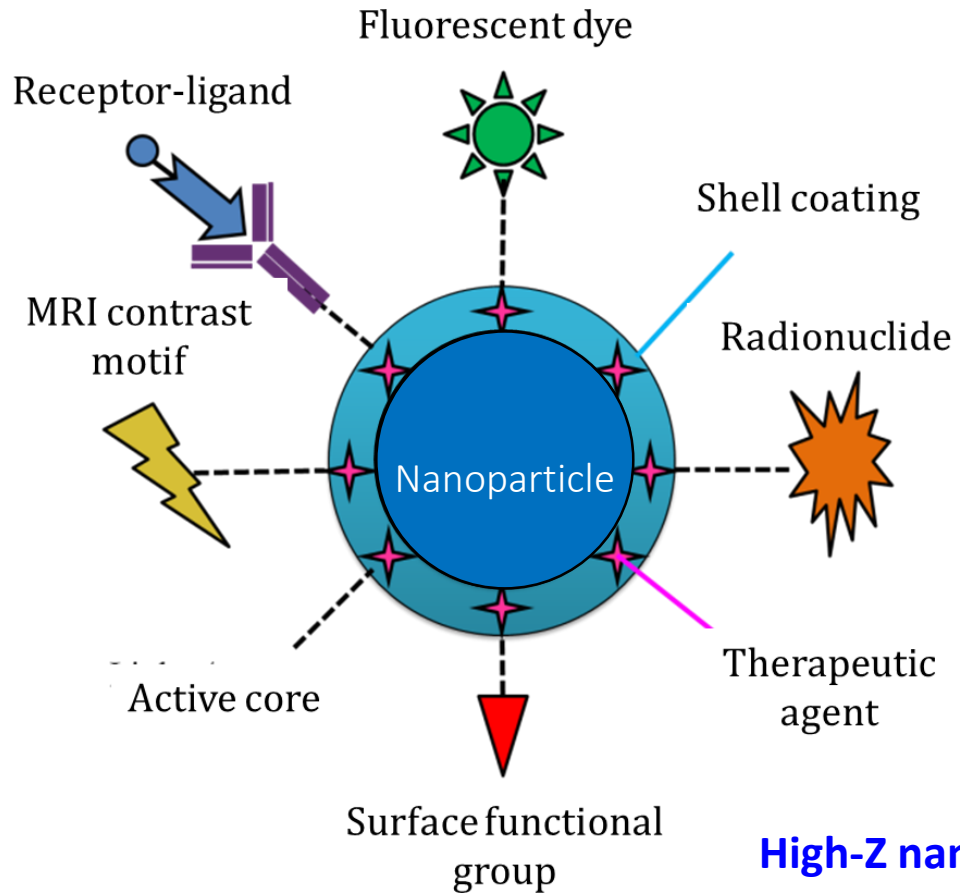
Université Paris Sud, CNRS, 91405, Orsay Cedex, France

Institut des Sciences Moléculaires d'Orsay (ISMO, UMR 8214)

erika.porcel@u-psud.fr



Advantages of nanoparticles



Surface chemistry
Versatility
Multi-modality

Different applications:

- Drug delivery (anticancer drugs)
- Medical imaging...

Objective:

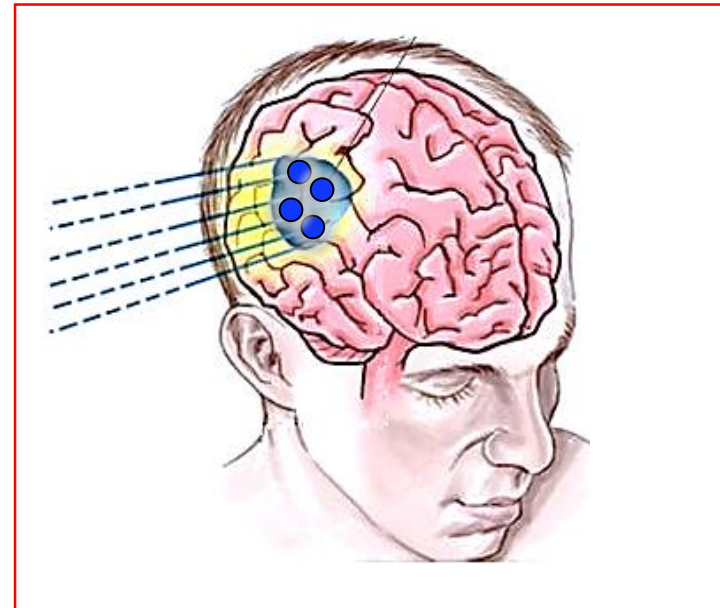
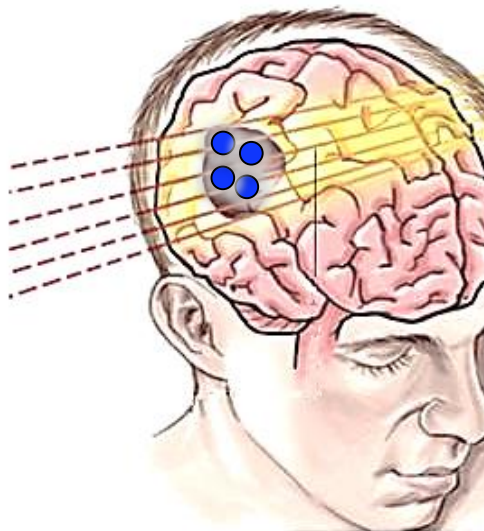
Metal NPs
+
Radiation therapies

High-Z nano-agent:

- Small (<10 nm) ...for accumulation in tumors by EPR
- Biocompatible & not toxic
- Optical, electronic , magnetic properties
- Diverse surface chemistry

New strategy

Addition of high-Z based nanoparticles

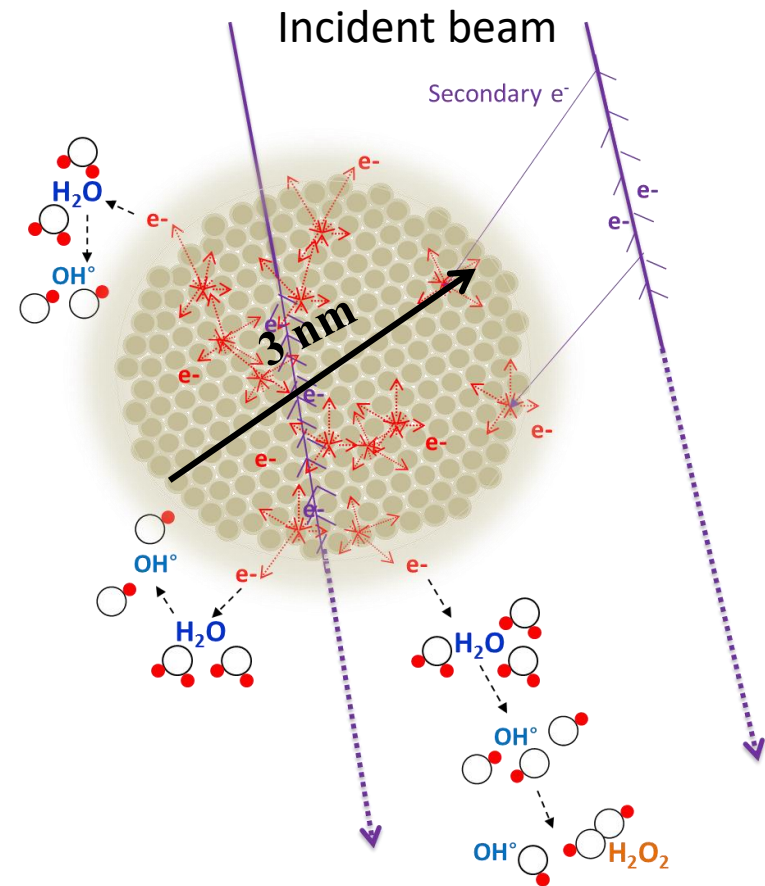
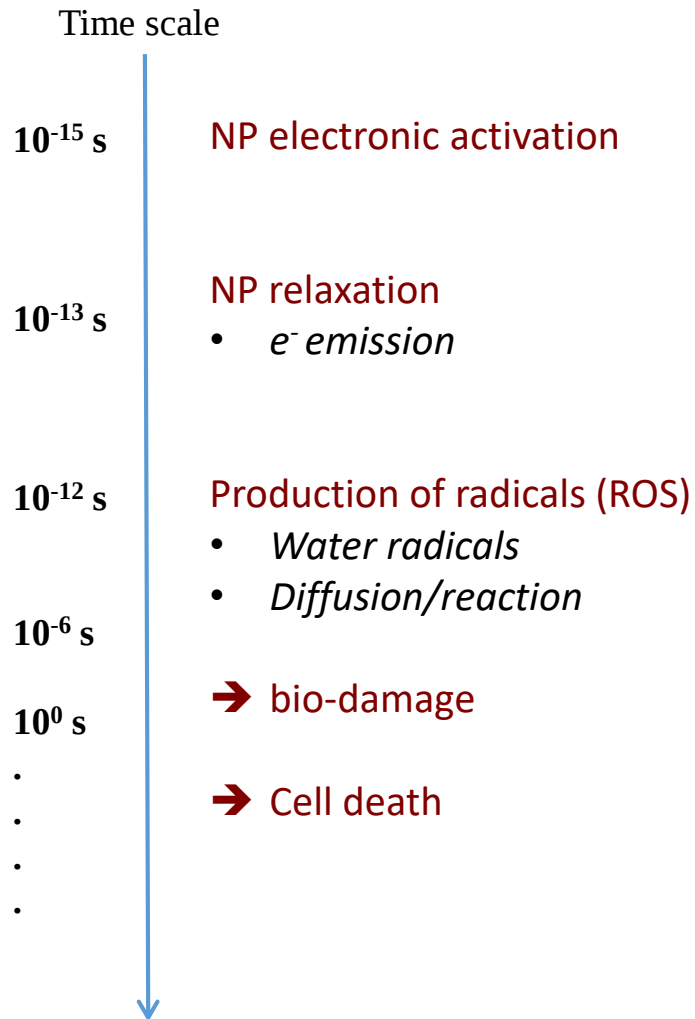


- Accumulation of NPs in the tumor
- Local increase of the radiation effect

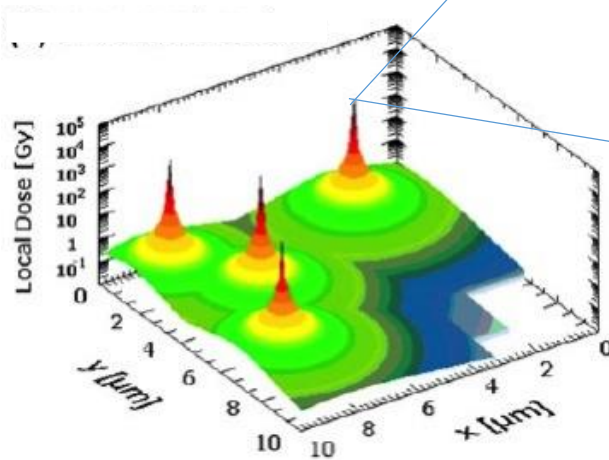
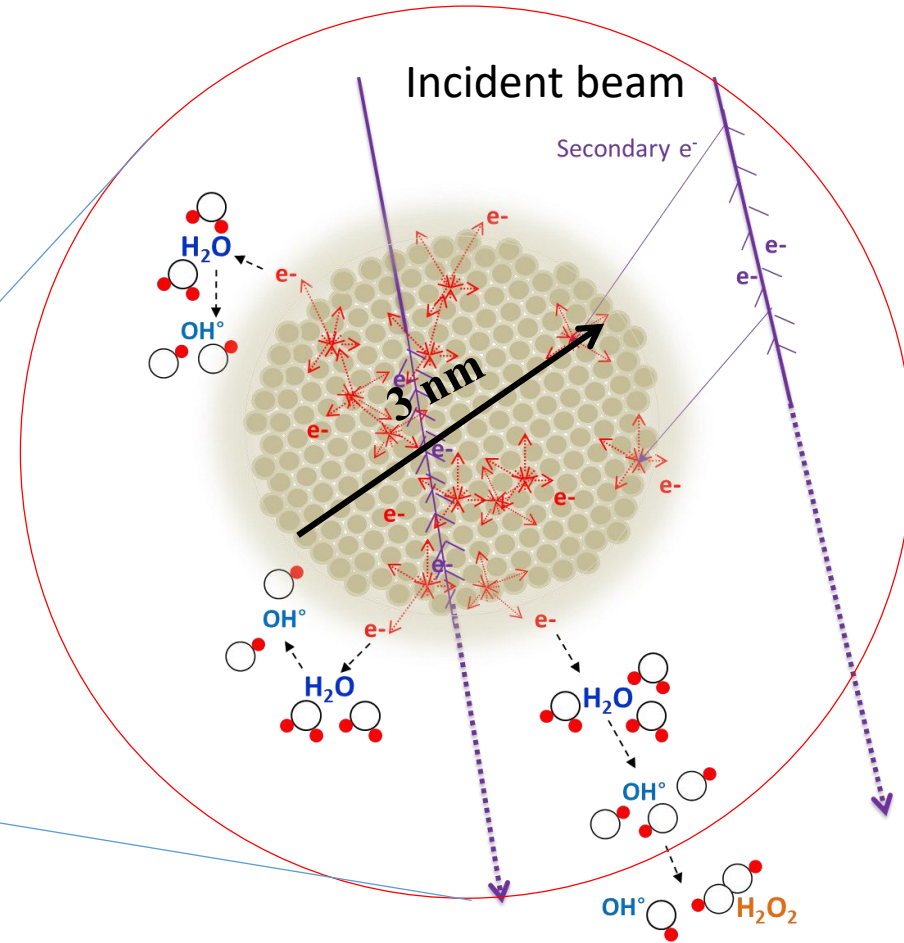
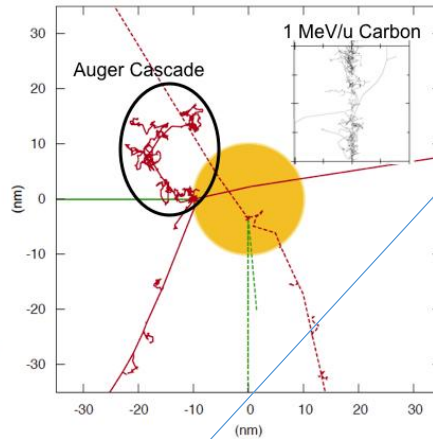
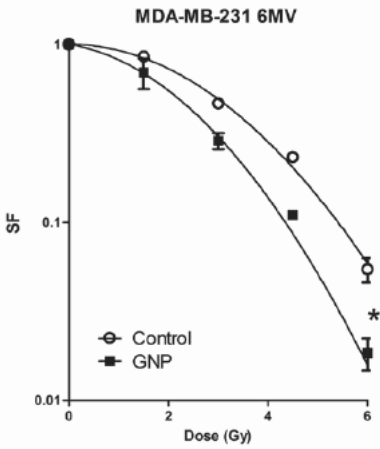
Therefore, reduction of the total dose

Lacombe S, Porcel E and Scifoni E.
Cancer Nanotechnology, vol. 8(1), (2017)

Nanoscale mechanisms



Local Effect Model



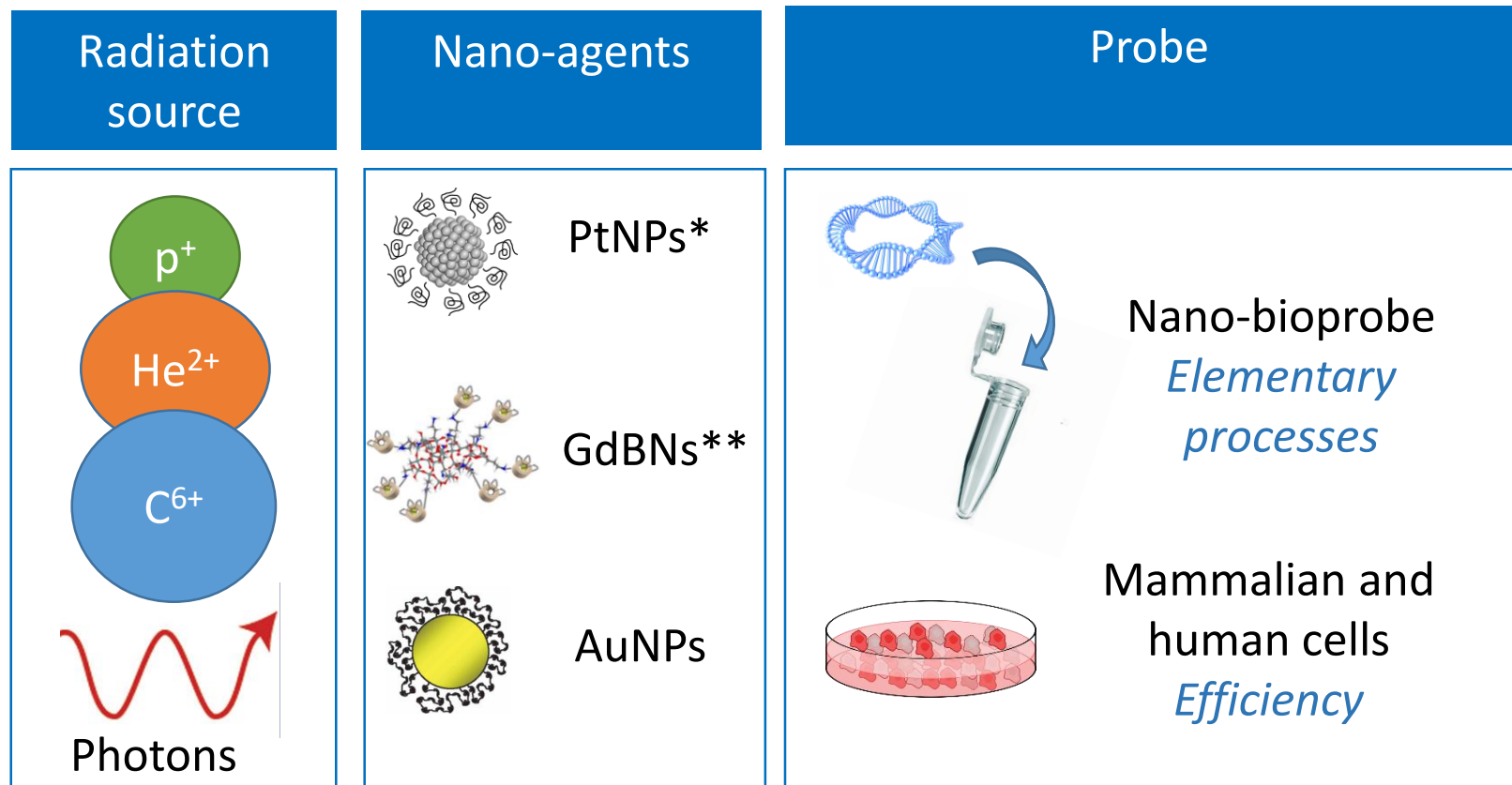
- Confined nano-size perturbation
- Same size as biomolecules

➤ NP effect = induction of local dose « spikes »

Expertise: ions + NPs

Small metallic NPs (Pt, AU, Gd) / **ions** (high energy)

Multiscale approach



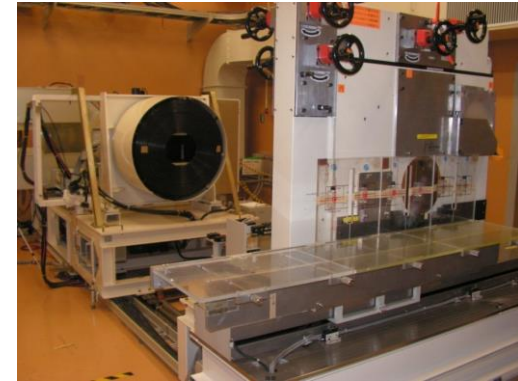
Irradiation facilities

- Fast ion medical beam (HIMAC, Chiba, Japon)

Uniform Scanning (SOBP)

C^{6+} (290MeV/u)

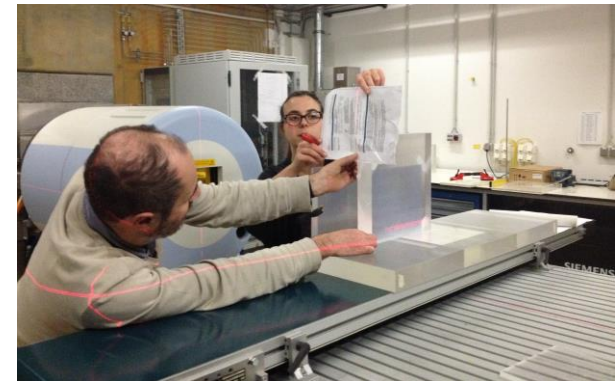
He^{2+} (150MeV/u)



- Fast ion medical beam (HIT, Germany)

Pencil Beam

C^{6+} (290MeV/u)



- Proton beam (KVI, The Netherlands)

Pristine peak

150 MeV

- Gamma rays Cs137 (Curie, Orsay, France)

Small Platinum NPs - PEG

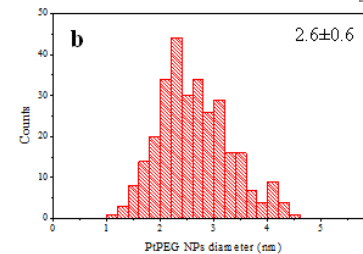
*French patent: FR1900008

Synthesis by **radiolysis**

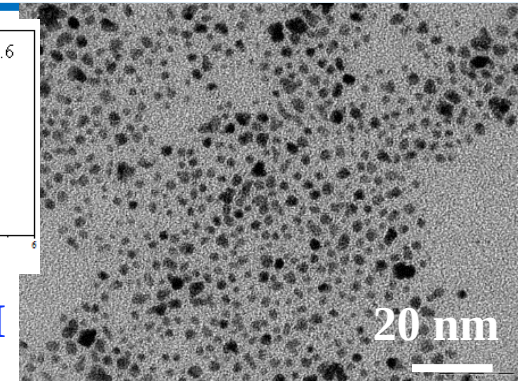
water + Pt salt irradiated by γ -rays

➤ **Green chemistry**

(coll. H. Remita, ICP, Orsay)



TEM



- ✓ Small (3 nm) for internalization by **EPR** effect (Enhanced Permeability Retention)
- ✓ Biocompatible, stable
- ✓ Sterile solution (ready to use)

Small Platinum NPs - PEG

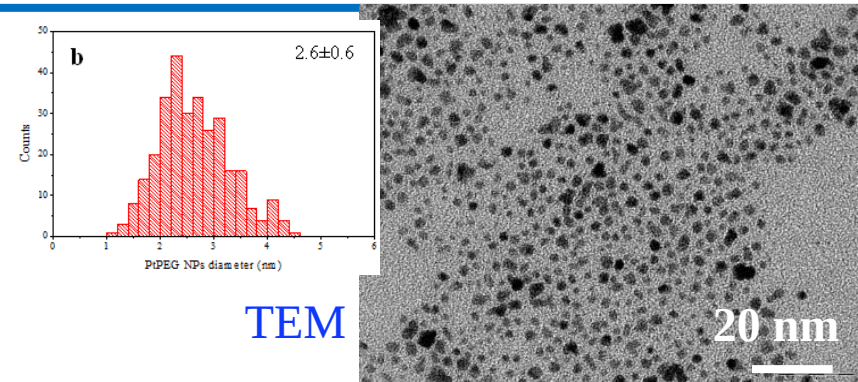
Synthesis by **radiolysis**

water + Pt salt irradiated by γ -rays

➤ **Green chemistry**

(coll. H. Remita, ICP, Orsay)

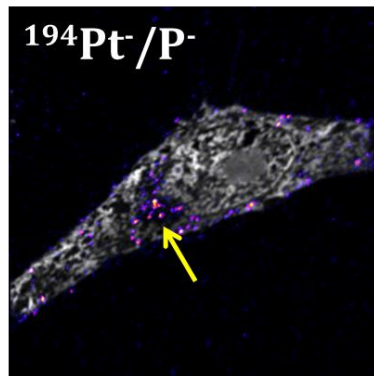
**French patent: FR1900008*



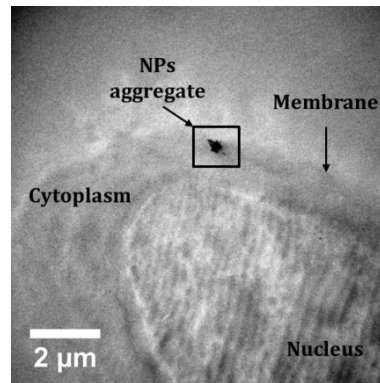
TEM

20 nm

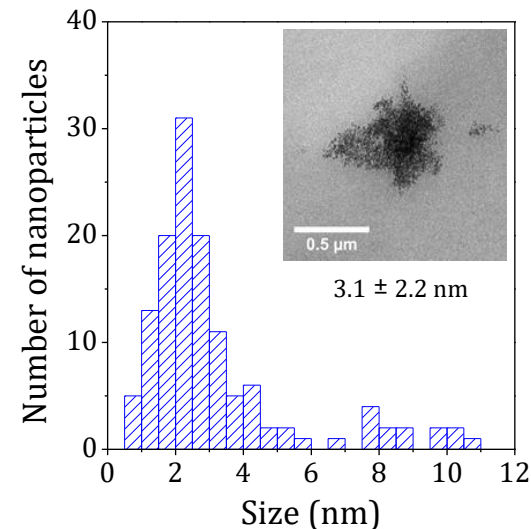
- ✓ Small (3 nm) for internalization by **EPR** effect (Enhanced Permeability Retention)
- ✓ Biocompatible, stable
- ✓ Sterile solution (ready to use)



NanoSIMS



TEM

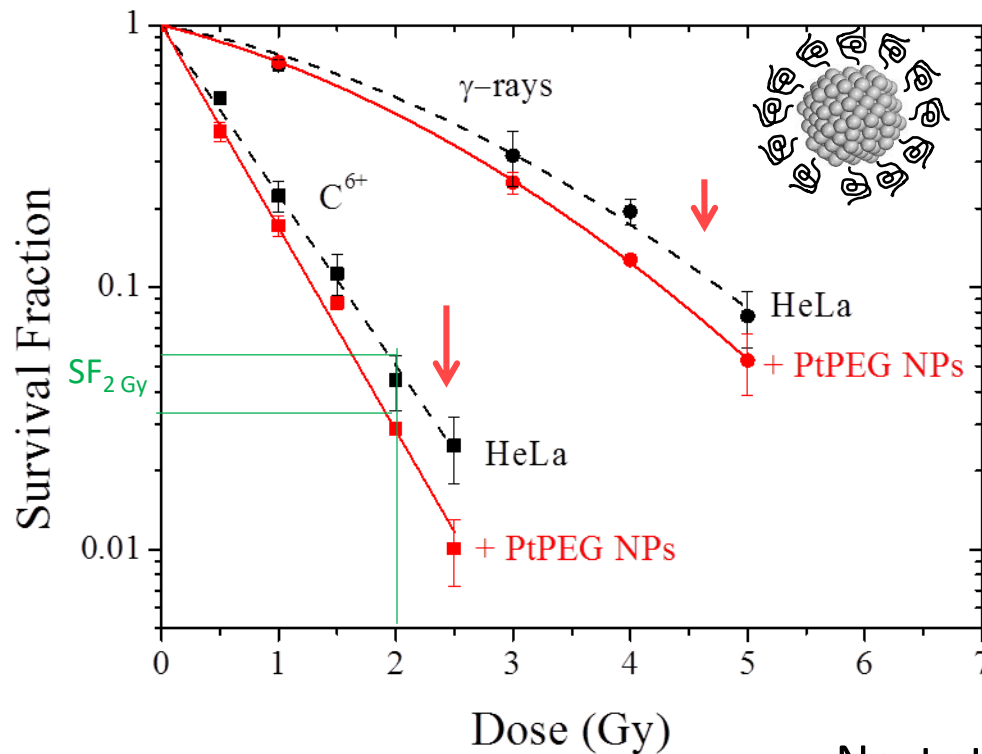


PtNP-PEG are localized exclusively in the **cytoplasm**

Effects of PtNPs-PEG

Irradiation C^{6+} (SOBP) and gamma rays /HeLa cells

Incubation : 0.5 mM Pt, 6h

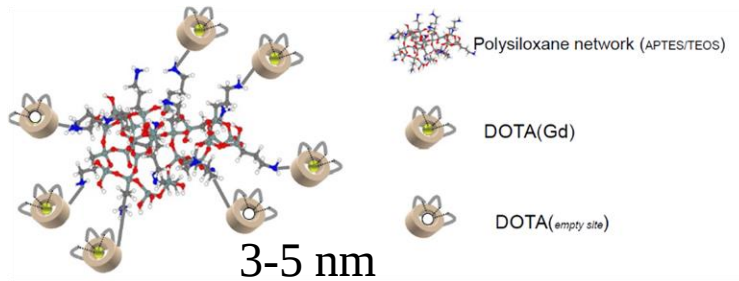


SF 2Gy	
γ -rays	14%
C^{6+} (SOBP)	42%

➤ Enhancement of carbon ion efficiency

Next step: Towards multimodality/theranostic

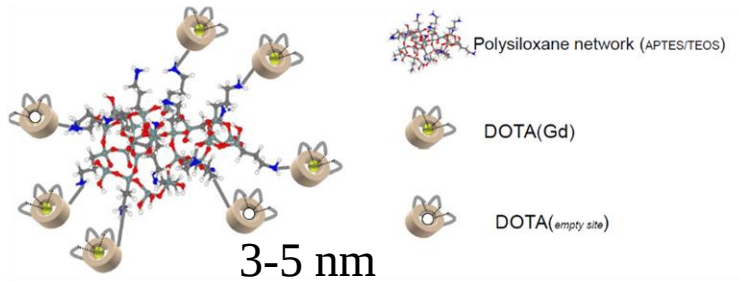
Gadolinium-based NPs (GdBN)



- ✓ MRI active
- ✓ High colloidal stability and freeze drying ability
- ✓ *In vivo*: rapid elimination by the kidneys, no evidence of toxicity

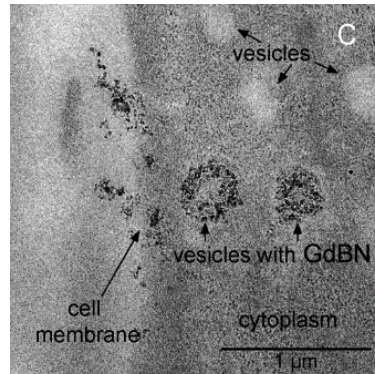
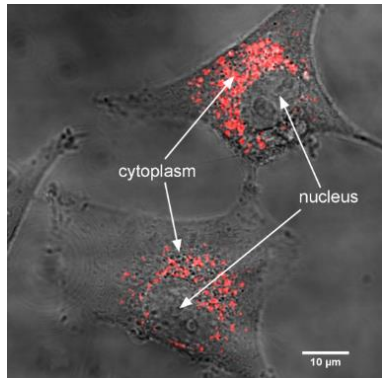
 Coll. O. TILLEMENT (Lyon 1)

Gadolinium-based NPs (GdBN)



- ✓ MRI active
- ✓ High colloidal stability and freeze drying ability
- ✓ *In vivo*: rapid elimination by the kidneys, no evidence of toxicity

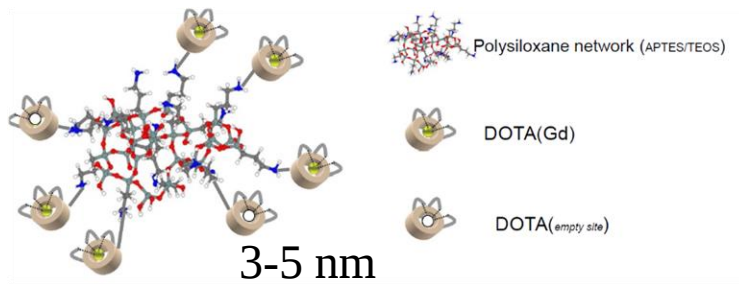
 Coll. O. TILLEMENT (Lyon 1)



Porcel et al, Nanomedicine NMB 10:8 (2014)

Lux et al BJR 91 (2018)

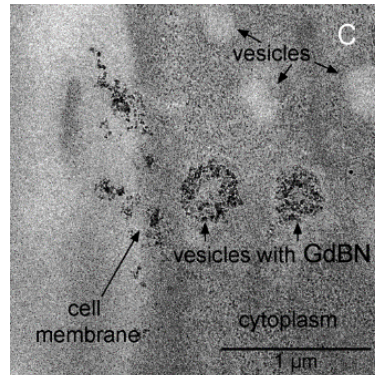
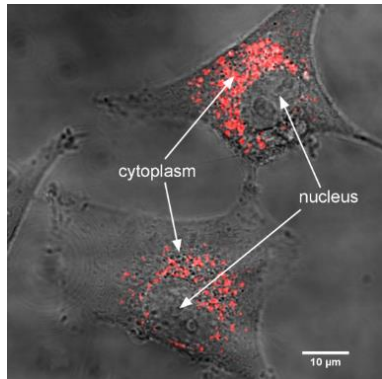
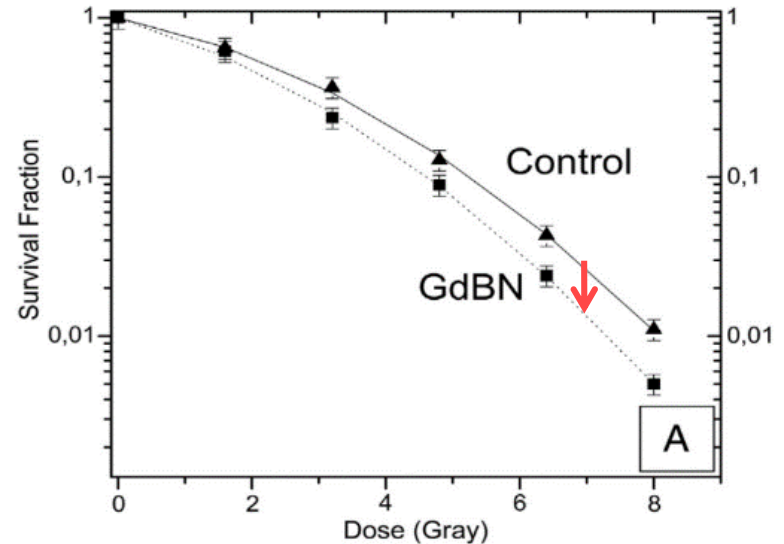
Gadolinium-based NPs (GdBN)



- ✓ MRI active
- ✓ High colloidal stability and freeze drying ability
- ✓ *In vivo*: rapid elimination by the kidneys, no evidence of toxicity

 Coll. O. TILLEMENT (Lyon 1)

Irradiation C^{6+} (entrance)/ CHO cells
Incubation : 1 mM Gd, 6h



SER(SF 2Gy)

C^{6+}
(SOBP)

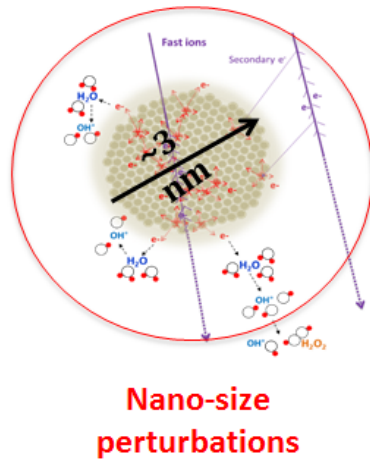
17%

- Effect (even low) with GdBNs
- Towards **theranostic** with carbon ion

Porcel et al, Nanomedicine NMB 10:8 (2014)
Sancey et al BJR 87:1041 (2014)

What did we learn ?

...towards prediction...



Time scale

10^{-15} s	Activation of NP Incident ions and 2ry e^- produced along the particle track activate NPs by Coulomb interactions / plasmon effect
10^{-13} s	NP relaxation e^- emission (out) e^- capture to neutralize the NP (in)
10^{-6} s	Production of radicals Reactive nanoclusters
10^0 s	Biodamage
.	Cell death

PHYSICAL STEP

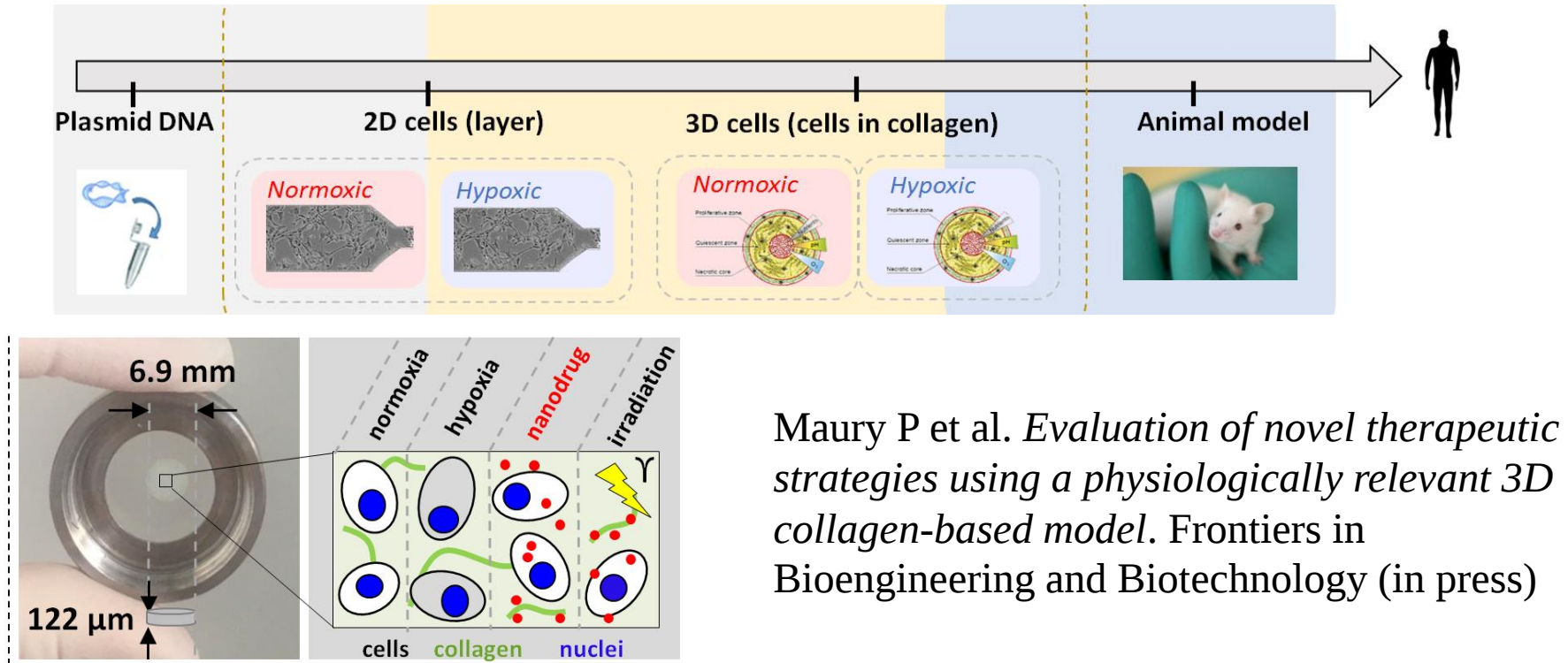
CHEMICAL STEP

BIOLOGICAL STEP

Need to be considered

...multiparametric...

3D sample



Maury P et al. *Evaluation of novel therapeutic strategies using a physiologically relevant 3D collagen-based model*. Frontiers in Bioengineering and Biotechnology (in press)

Study of the key parameters in the radioenhancement effect using 3D sample :
LET, ion nature, nanomaterial, cell line, environment....

Aknowledgments

Contact:

erika.porcel@universite-paris-saclay.fr



Previous group members:

Xiaomin YANG

Daniela Salado

Lenka Stefancikova

Marta Bolsa-Ferruz

Xue Li

Our team:

Sandrine Lacombe

Erika Porcel

Pauline Maury

Cesar Gonzalez

Charles Bapaume

Collaborations

R. Hirayama (NIRS, HIMAC, Chiba, Japan)

H. Remita (LCP, Univ. Paris Sud, Orsay, France)

O. Tillement (LPCML, Lyon, France)

S. Roux (UTINAM, Besançon, France)



université
PARIS-SACLAY

