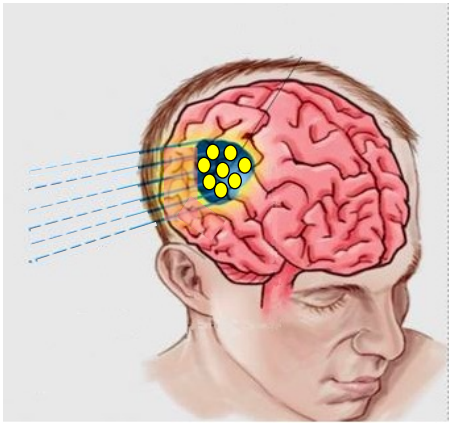
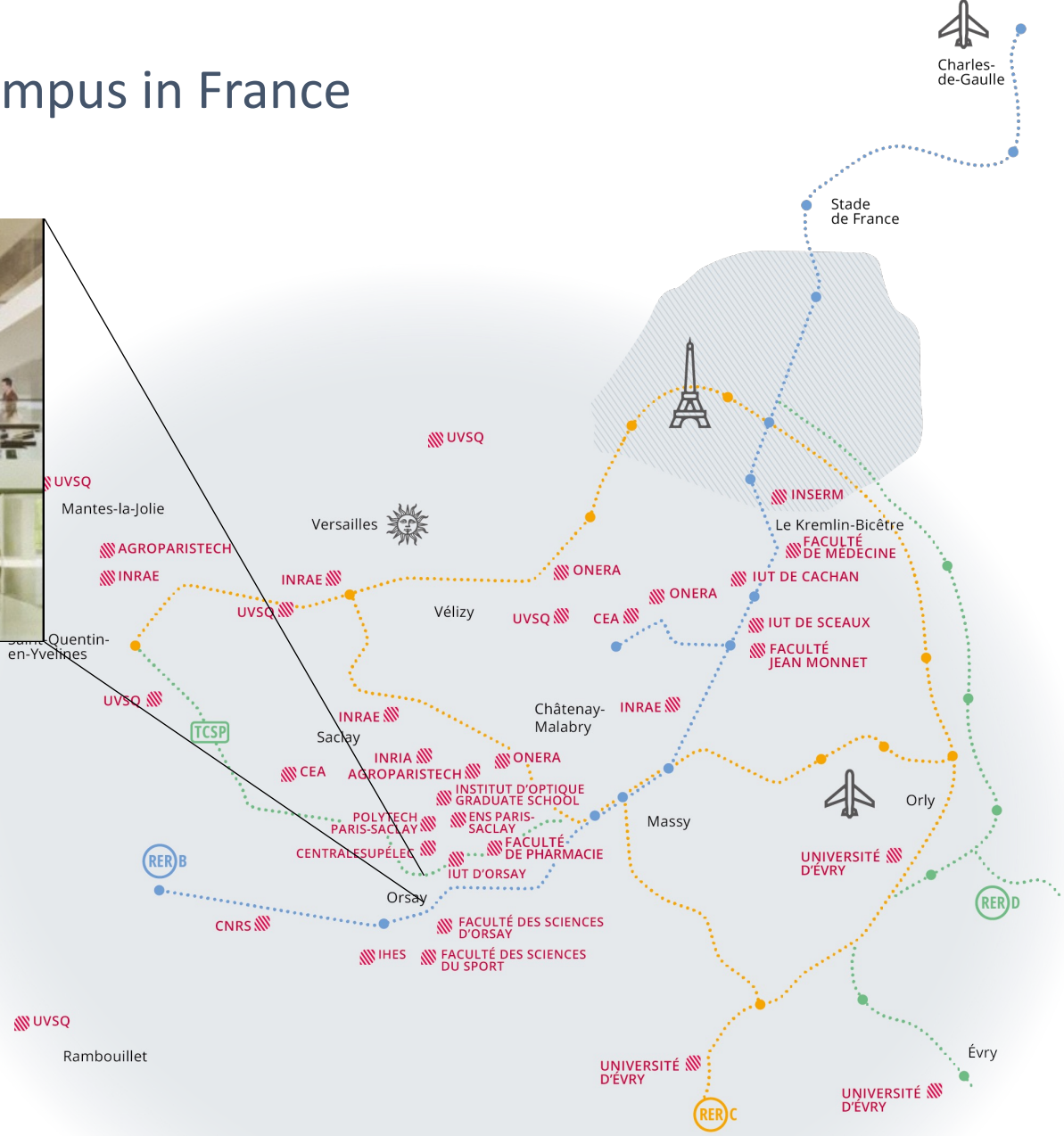
Refresh course ECMP

Nanoparticles in diagnostics and therapy

Sandrine LACOMBE, Prof, Hab.
Univ. Paris Saclay, CNRS, Orsay, France



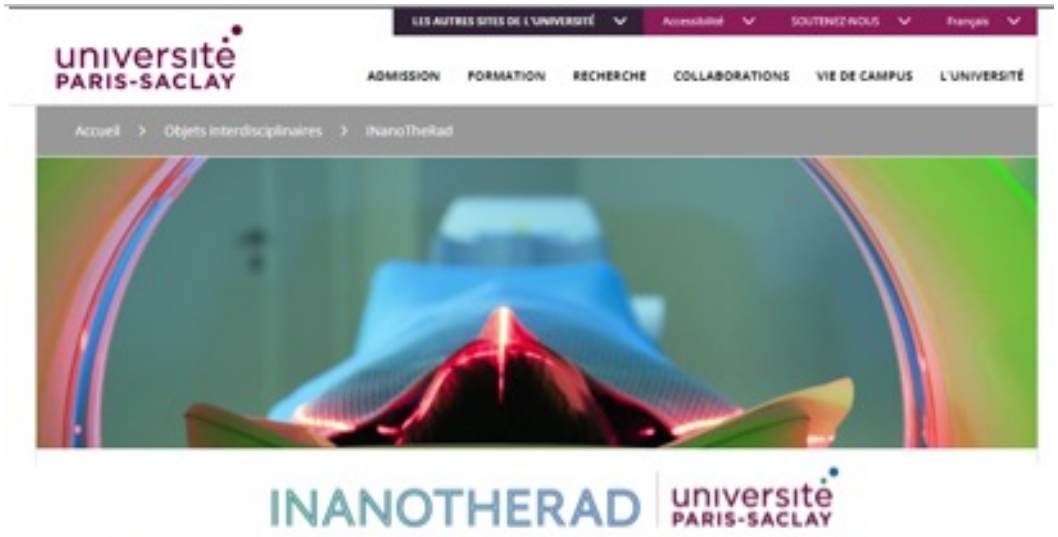
U. Paris Saclay: largest campus in France
ARWU: 12; 1st in EU



ISMO
Institut des sciences moléculaires d'Orsay

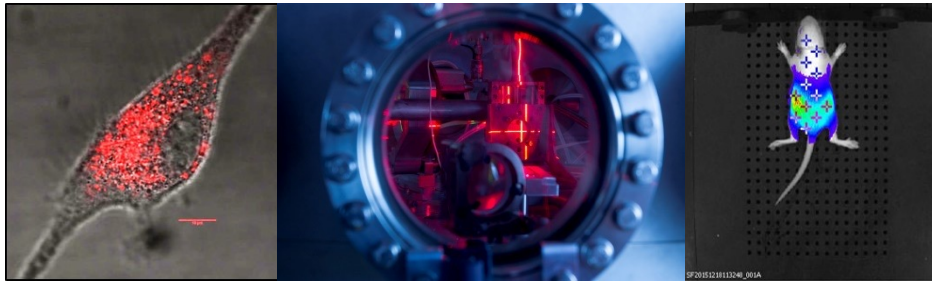
université PARIS-SACLAY

Interdisciplinary center of **Nano**technologies and innovative **The**rapies with **Rad**iations to treat cancer



https://www.universite-paris-saclay.fr/en/objets-interdisciplinaires/inanotherad

- 2 excellence centers of cancer research (Institute Gustave Roussy, Institute Curie)
- >15 labs, 150 researchers
- Multidisciplinary research, education, clinic
- Workshops and events



Contact: Elodie.carpentier@universite-paris-saclay.fr
Coordinator : Sandrine Lacombe

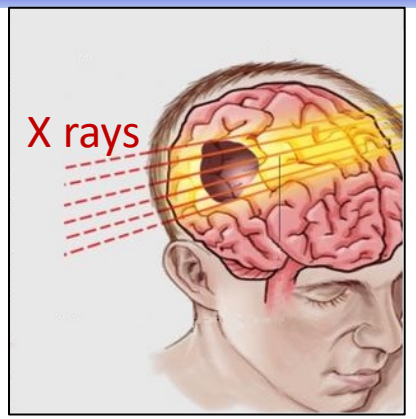
Motivation

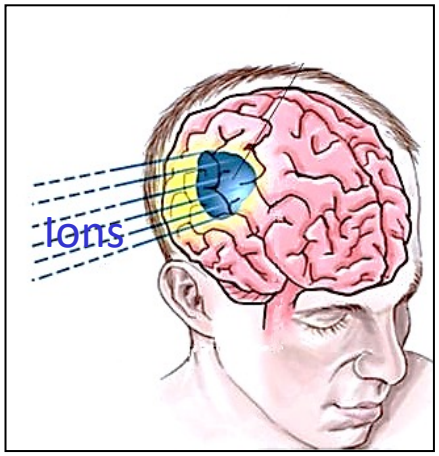
Radiotherapy : x-rays/γ-rays traverse the body

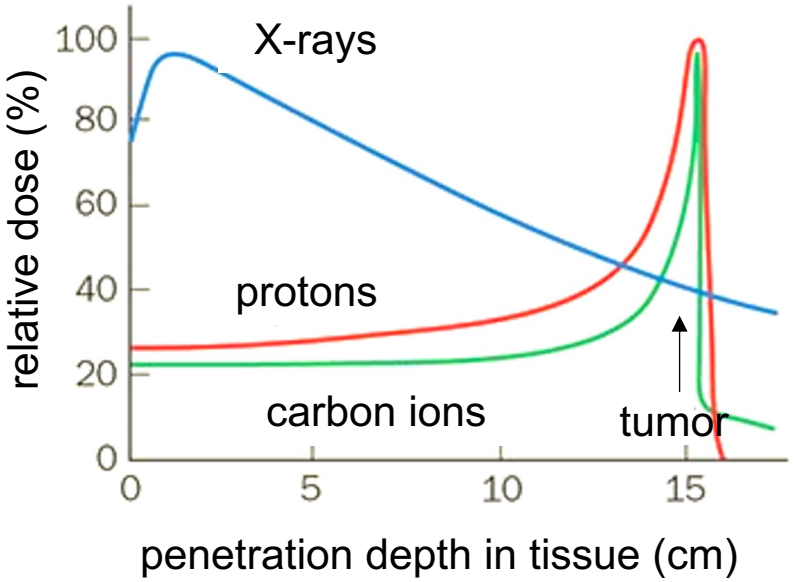
50% of the patients
Non invasive but **side effects and radioresistance**

➢ New modalities to improve tumor targeting :

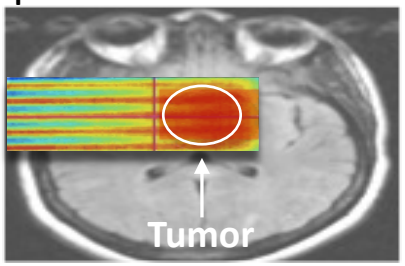
Ex: particle therapy, proton microbeams, FLASH (ultra high dose rate), VHEE (Very High Energy Electrons), Image guided RT …





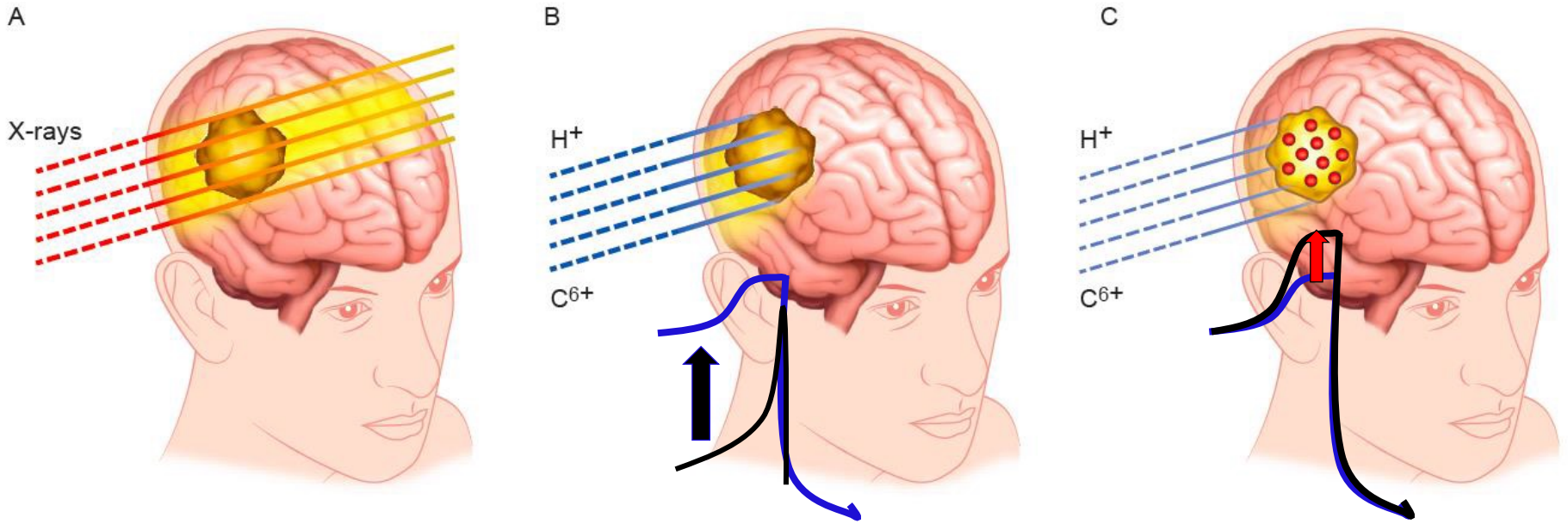


proton microbeams



Prezado et al. 2013

Challenges



➔ **Increase RBE <u>at the tumor</u>**

➔ Decrease the total dose ad thus damage at the entrance of the track

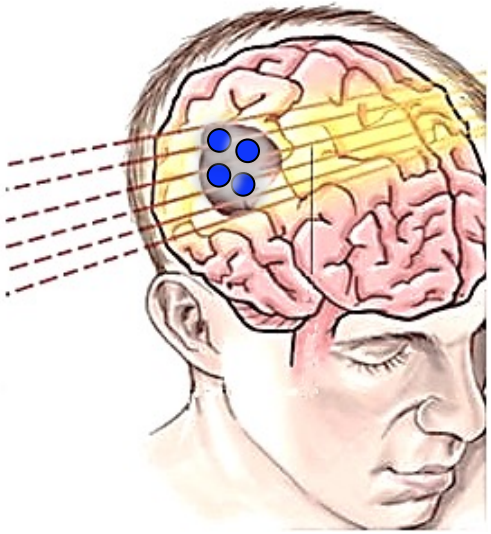
How???

Lacombe & Scifoni, Cancer Nanotech.8:9 (2017)

Improvement of RT with theranostic nanoparticles (NPs)

How to improve radiation effects at the tumor?

- Sensitization of cells to radiation (radiosensitization) with drugs
- Amplification of electron emision at the tumor (**radioenhancement**)
- Improvement of **diagnostic**



How to induce **radio-enhancement** (= improve e- emission) ?

➢ Bring **high-Z** elements at the tumor

Why **nanoparticles (NPs) :**

To bring **multimodality with the same nanoagent** to both image/diagnose the tumor and increase RBE at tumor

➔ **theranostic** = enhancement of radiation effect + medical imaging

Anselmo AC & Mitragotri S.. Nanoparticles in the clinic: An update. Bioeng Transl Med. (2019)

Early stage - Nanoscale mechanisms

Time scale

10^{-15} s — NP electronic activation

10^{-13} s — NP relaxation
- *e^- emission*

10^{-12} s — Production of radicals (ROS)

10^{-6} s
- *Water radicals*
- *Diffusion/reaction*

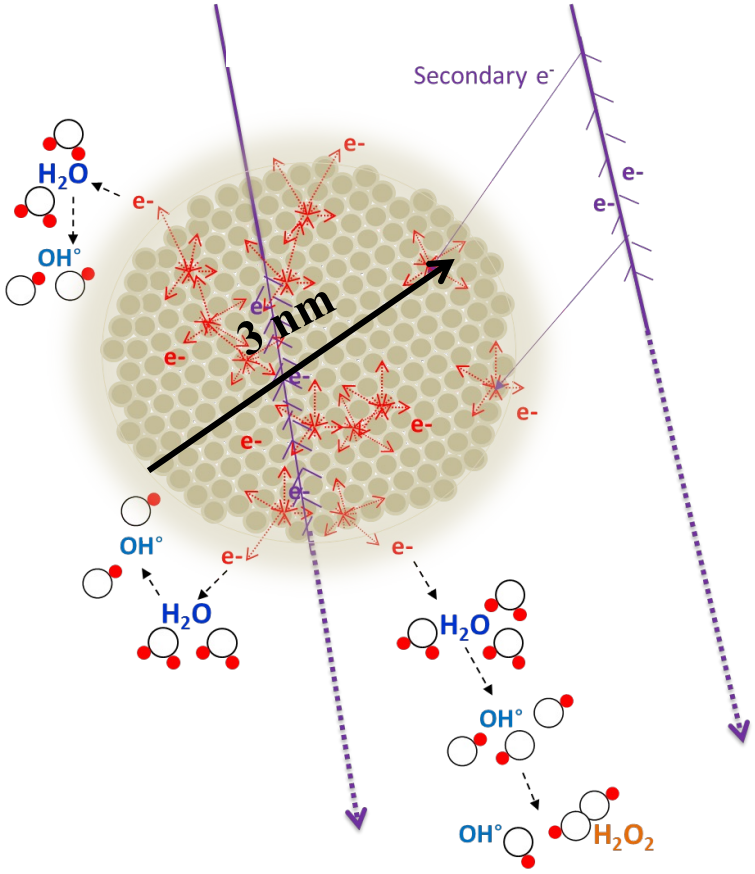
10^{0} s

. . . .

➔ bio-damage

➔ Cell death

Incident beam: photons, ions, e-



Foley, Guo et al., Chem Comm (2005)
Kobayashi et al Mutation Research (2010)
Porcel et al Nanotechnology (2010)

How does radioenhancement work

Material:

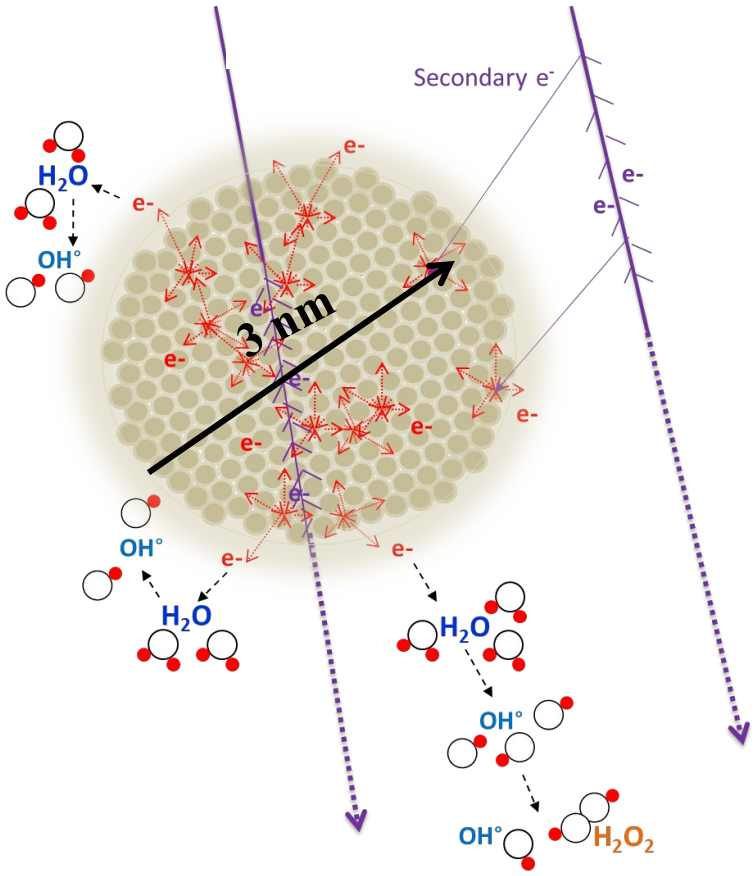
- **Good e-emitters: high Z** compounds

  Ex: Au (79), Gd (64), Hf (72), Fe (26) also Pt (78)

Design:

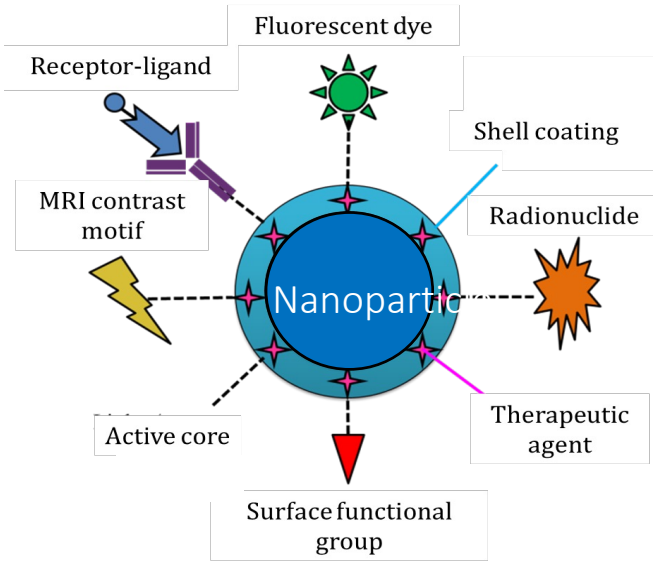
- Metallic (AuNP) or oxides (HfO2) NPs Inorganic macromolecules (AGuiX, MOFs..)
- Micelles able to carry Metal/oxide

Incident beam: photons, ions, e-



Multomodality of NPs

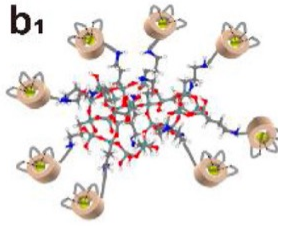
- ✓ Rich surface chemistry :
  - with **high Z materials** (ex: Au, Fe, Bi, Pt,)
  - **Contrast agents** (ex: Gd for MRI)
  - Radioisotopes (Zr for PET)
  - **drugs** (ex: gemcitabin, …)
  - Fluorescent tags (optical microscopy)

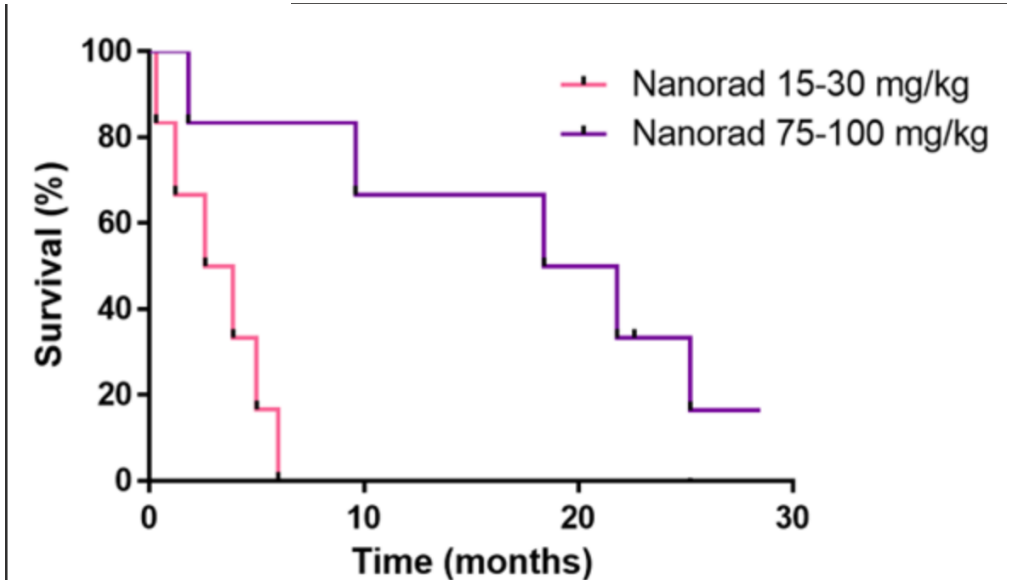


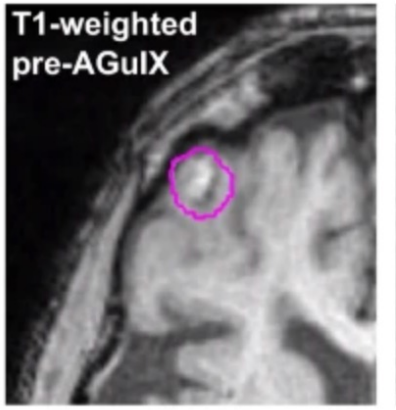
Wang R et al. Journal of Nanomaterials 2012
Rizzo L et al. Curr Opin Biotechnol 2013

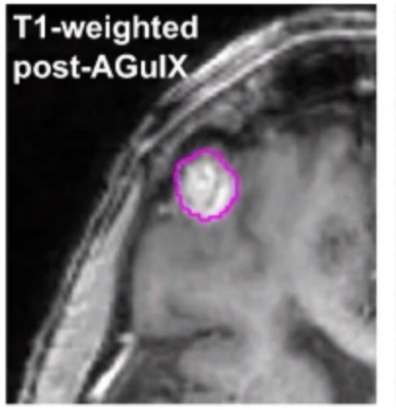
Clinical trials NP in RT – example

Gadolinium based nanoagent - AGuIX– (@NHTheraguix) – IV injection





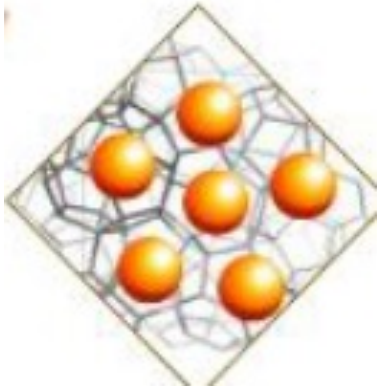




Courtesy R. Berbecco (D.F hospital, Boston), O. Tillement (Lyon 1)

Verry et al., Radiotherapy and Oncology 2021

Clinical trials NP in RT – example



- **gold** NPs – AuroShell (head & neck)
- SPIONs & **iron** oxide (pancreas)
- **hafnium oxide** NPs- NBTXR3 (@Nanobiotix) - IT injection

Bonvalot et al, Lancet Oncol 2019

NBTXR3, a first-in-class radioenhancer hafnium oxide nanoparticle, plus radiotherapy versus radiotherapy alone in patients with locally advanced soft-tissue sarcoma (Act.In.Sarc): a multicentre, phase 2–3, randomised, controlled trial

Towards multimodal treatment, image-guided RT, and personalization

Reviews: Anselmo. Bioeng. and transl. med. 2019

Smith et al Cancer Nanotechnoloy 2022, Gerken et al ChemRxiv. Cambridge 2023

Injection modalities

Intra tumoral injection:

-high concentration, high targeting

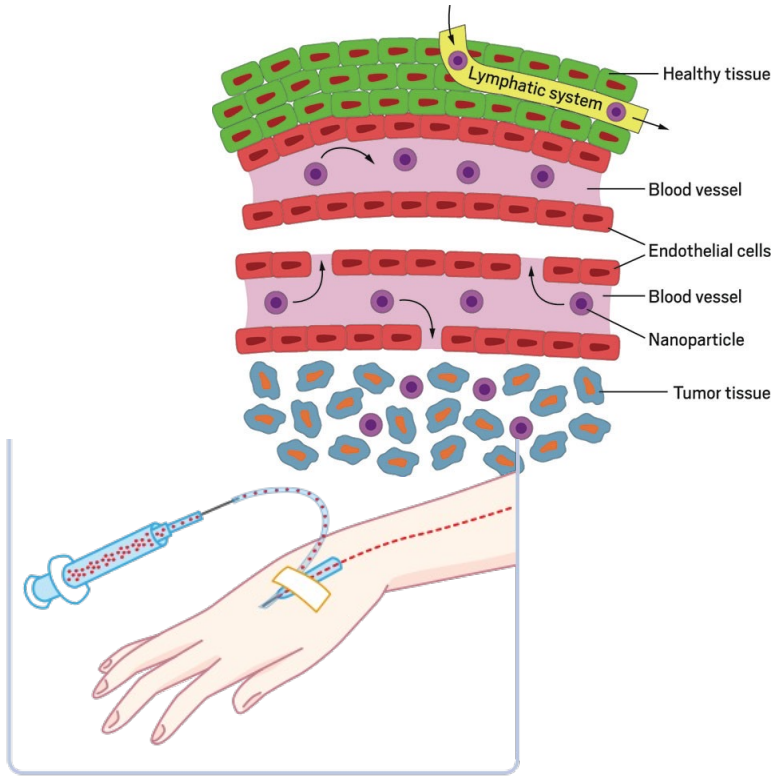
-but pain, no clearance, low repeatability

Intraveneous injection

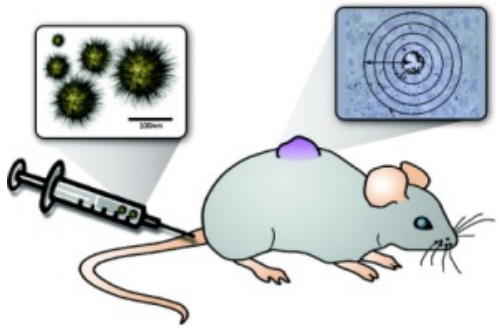
- low pain, repeatability
- Tumor concentration by EPR effect

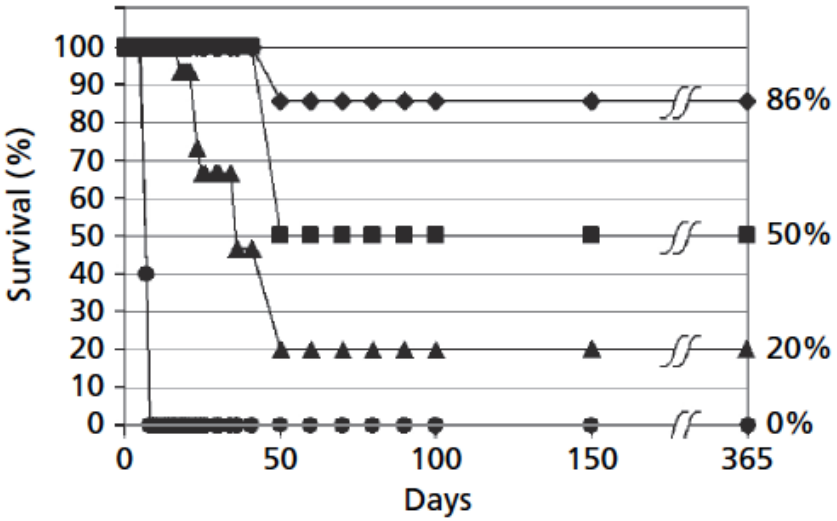
(Enhanced Permeability and Retention effet: NP<20 nm)

➢ low concentration but clearance and low toxicity



200 kV x-rays combined with AuNPs (2004)





AuNPs + RX

AuNPs + RX

X- rays

AuNP

Hainfeld et al., Phys Med Biol (2004)

Higher survival in the presence of AuNPs

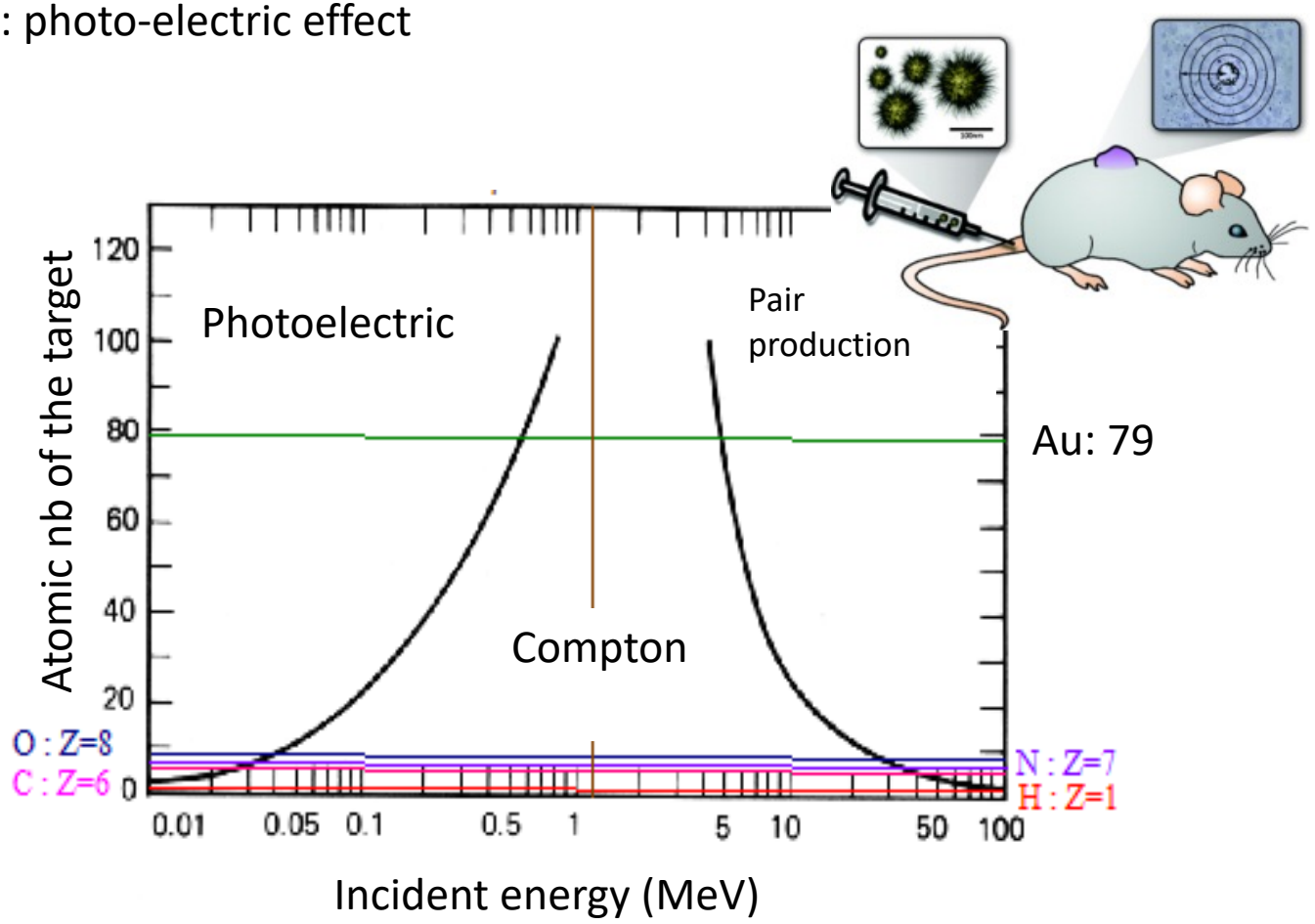
➢ Radioenhancement : amplification of radiation effect

Note: also observed with high-Z molecules

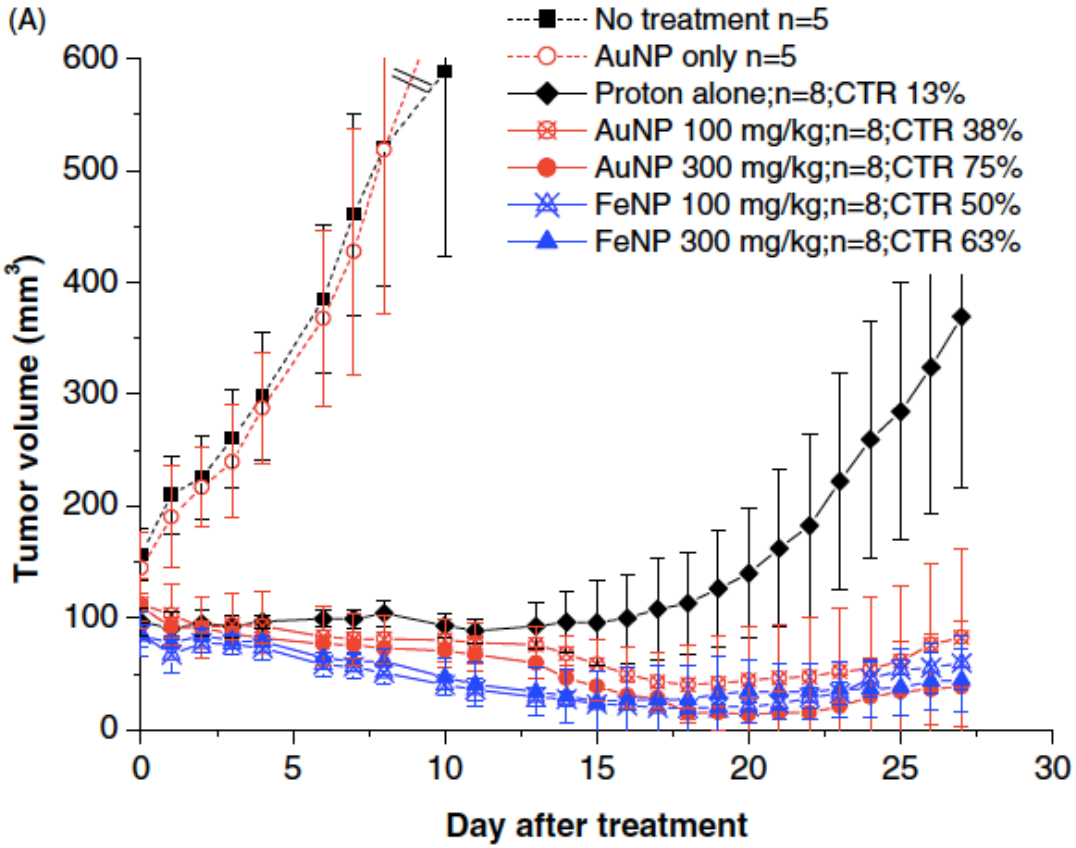
Kobayashi, LeSech et al, Rad.Res. ***2002***

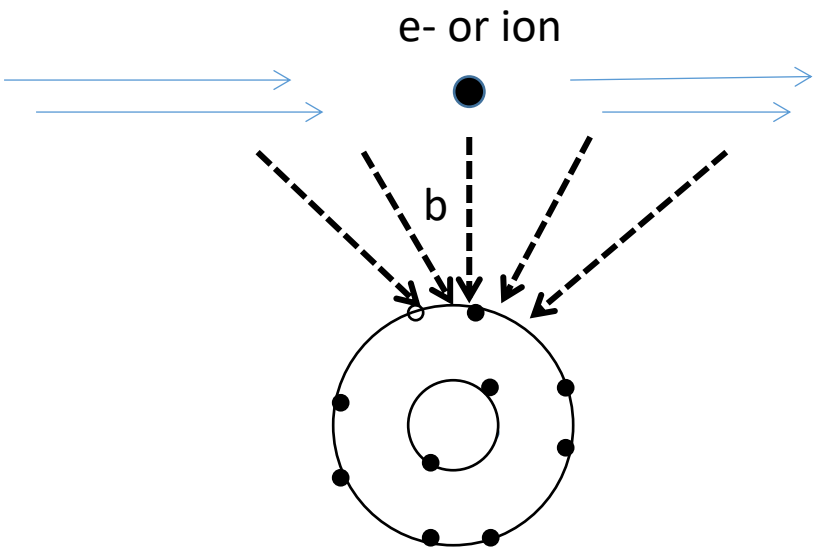
Proof of concept

Mechanism : photo-electric effect



Proof of concept with incident ions : 45 MeV proton beam combined with AuNPs, FeNPs





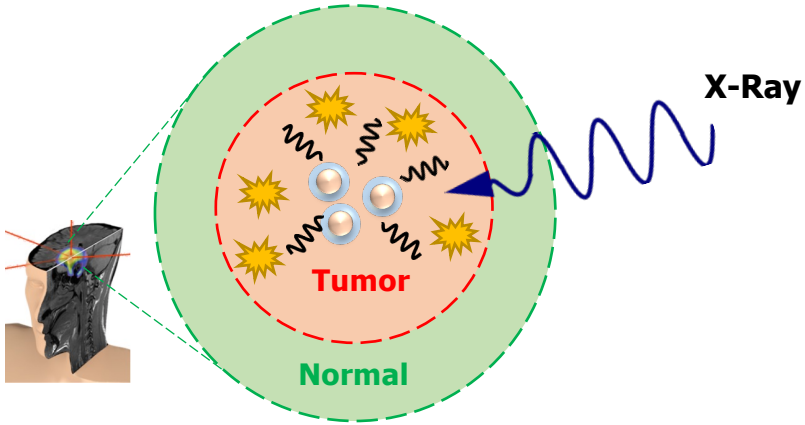
Decrease of the tumor volume in the presence of NPs

➢ NP radioenhancement effect with all types of incident radiation

Kim et al, Phys Med biol. 2012

Characteristics for NPs

- **Rich diversity in chemistry** (@environmental impact, low cost)
- **Stable in water and biological buffers**
- **Biocompatible & non toxic** (in cells but also in the blood stream)
- **Small size**: Compatible with IV (AGuiX: 4 nm)
- **Multimodal:** Electron emitter, Contrast agent, drug carrier…



Exemple of experimental roadmap for TH-NPs

- Synthesis, characterization of NPs
- in vitro (2D/3D) : Toxicity, localisation, and irradiation experiments
- in vivo : pharmacokinetics, toxicity, and irradiation experiments
- Prediction & modelisation/simulations: Quantification of nanoscale mechanisms
- Clinical trial

Radiation source	Targets
p^+ C^{6+} Photons	Nano-bioprobe *Elementary processes* Human cells 2D & 3D *Efficiency* In vivo *Toxicity* *localisation*

Exemple : development of platinum NPs (PtNPs)

Why Pt NPs :

- Platinum: Z=78 a good e- emitter,
- a compound already known by physicians (Cis Pt: chemotherapy)
- Small ~ 10 nm compatible with IV injection ⇢
- Biocompatibility, versatile, and adaptable to chemical functionalization

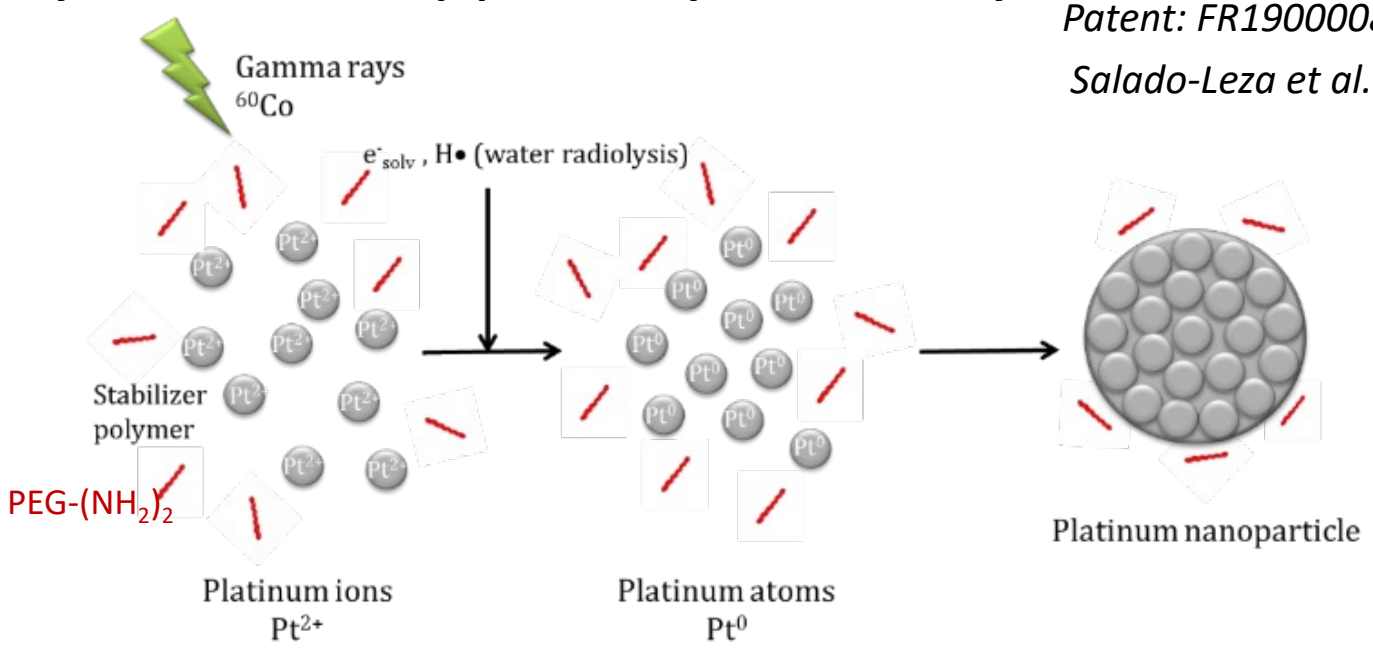
⇢ Functionalization with FDA approved PEG-$(NH2)_2$

Exemple : development of platinum NPs

Synthesis : one step process by water radiolysis

Patent: FR1900008 (in process for EU and US)

Salado-Leza et al. Nanotechnol Sci Appl. 2020



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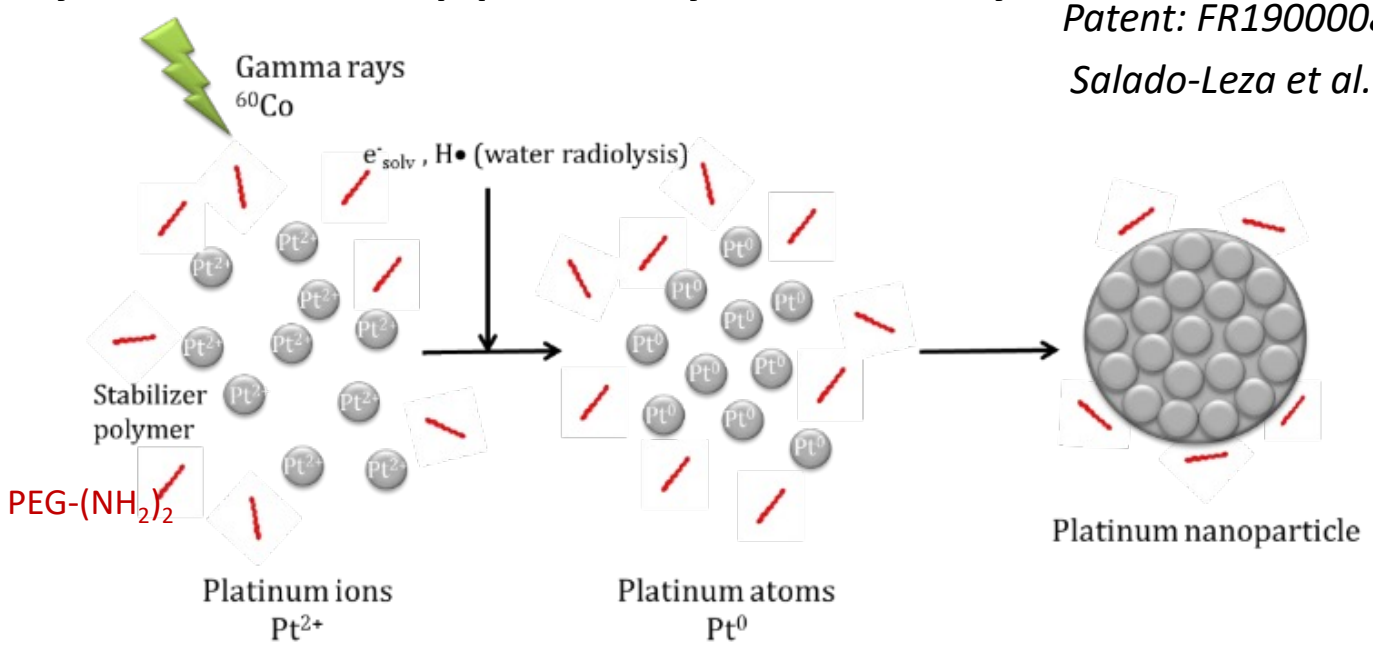
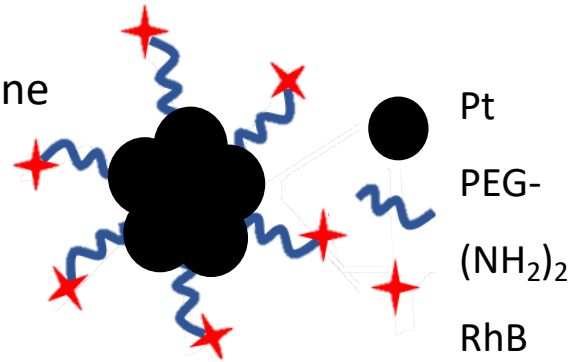


Possible attachement of a fluorescent tag @ PEG-$(NH2)_2$: rhodamine



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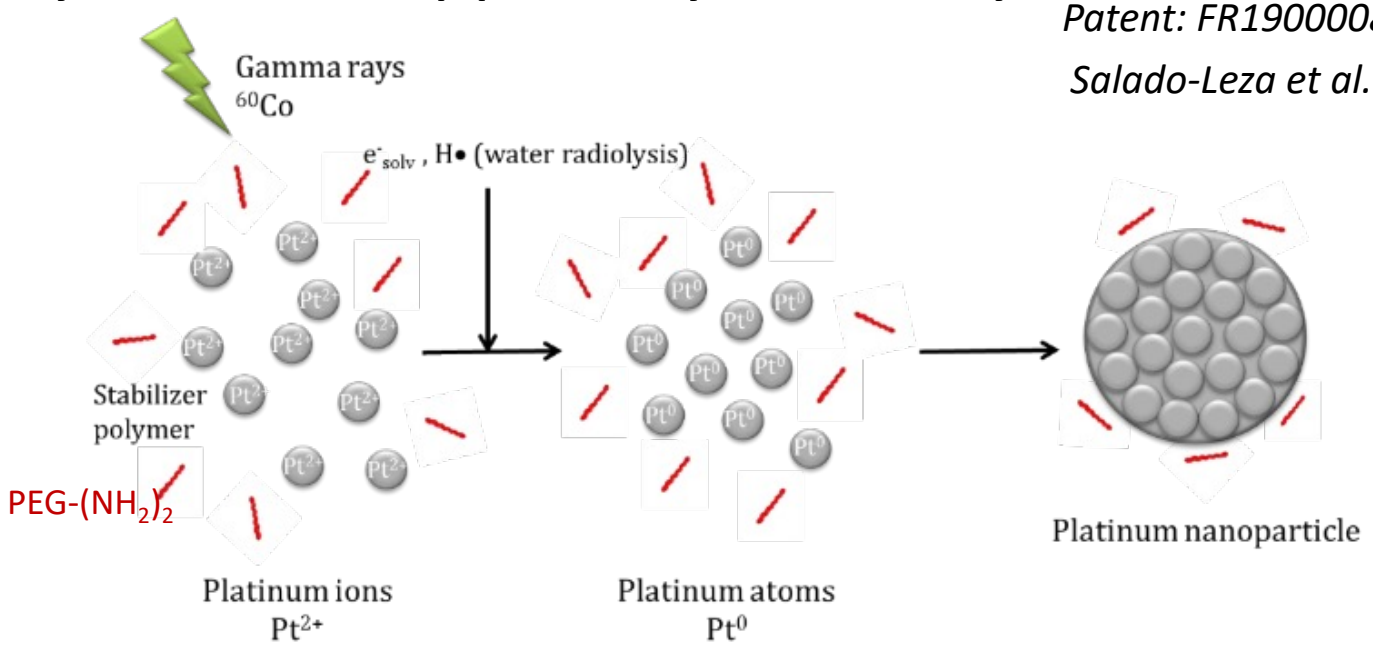

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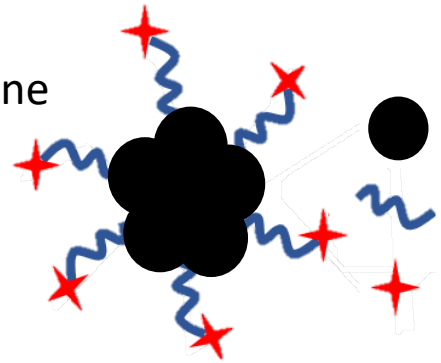


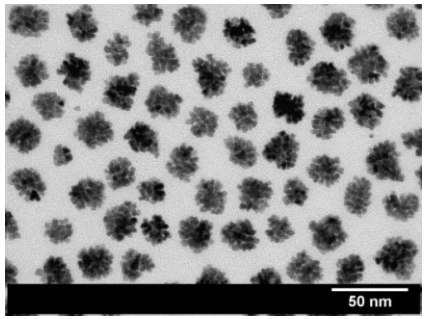
One pot synthesis of High performance

- Fast (1 step)
- Reproducible
- Green (no solvent)
- Low cost
- Efficicient : 100% rate and solution ready -to-use in clinic (sterilized by gamma radiation)

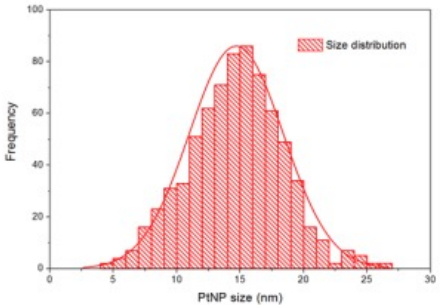
Exemple : development of platinum NPs

Characterization of PtNPs

Shape: TEM



size: DLS



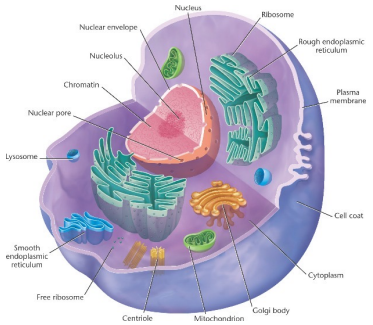
Yang, X. et al. Int. J. Mol. Sci. ***2020***

Salado-Leza D, Porcel E, et al. Nanotechnol Sci Appl. ***2020***

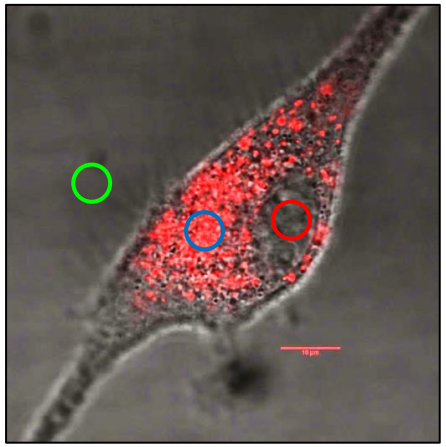
Exemple : development of platinum NPs

Cell uptake and Intracellular distribution in cells (2D)

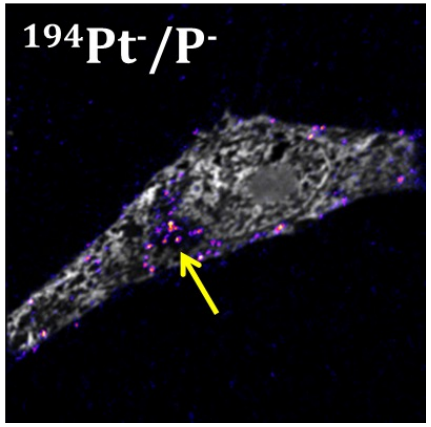
Techniques: confocal microscopy, TEM, Nano-SIMS …



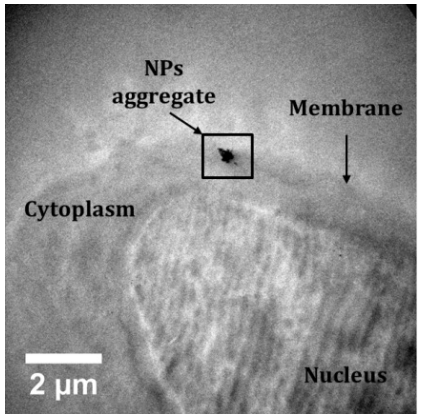
Quantification by ICP MS (ex:$5x10^5$ NPs per cell)



confocal



NanoSIMS



TEM

➢ **radioenhancers** are localized in the **cytoplasm**

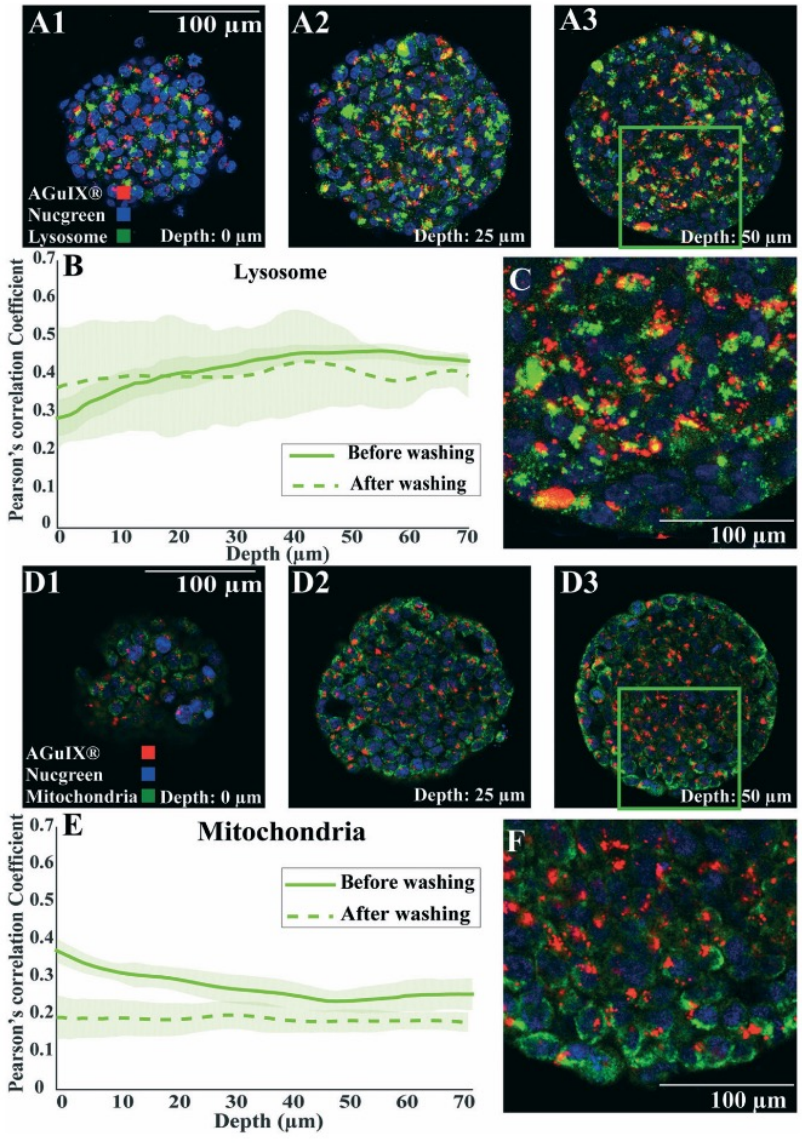
Salado-Leza D et al. Nanotechnology, science and applications (2020).

Exemple : development of platinum NPs

Cell uptake and intracellular distribution of AGuiX NPs in 3D cell model to mimic the tumor

Quantifying nanotherapeutic penetration using a hydrogel-based microsystem as a new 3D *in vitro* platform†

Saba Goodarzi, [a] Audrey Prunet,[a] Fabien Rossetti, [a] Guillaume Bort, [a] Olivier Tillement, [a] Erika Porcel, [b] Sandrine Lacombe,[b] Ting-Di Wu,[cd] Jean-Luc Guerquin-Kern, [cd] Hélène Delanoë-Ayari, [a] François Lux [ae] and Charlotte Rivière [*ae]



- NPs can travel through the **extra cellular matrix**
- then localize **in the cytoplasm**
- Same work in process with PtNPs (not yet published)

S. Goodarzi et al Lab Chip, 2021. DOI: 10.1039/d1lc00192b

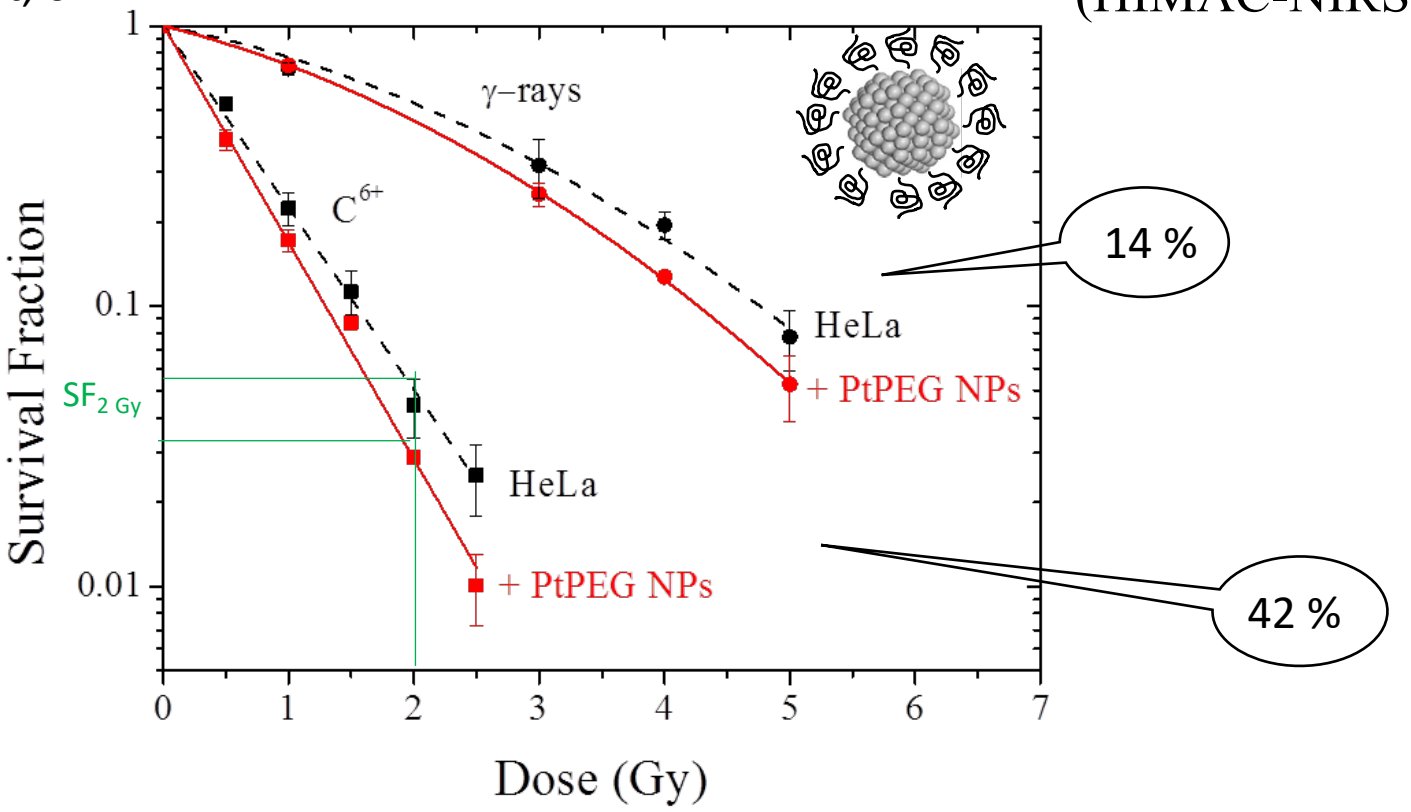
Not published - confidential

Exemple : development of platinum NPs

Radioenhancement : Irradiation by γ rays & **C^{6+} (SOBP: 400MeV/u)** on **HeLa** cells

Incubation : 0.5 mM Pt, 6h

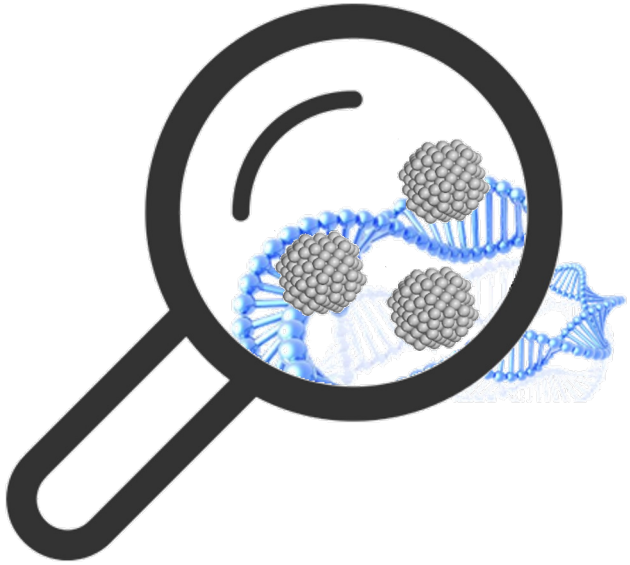
(HIMAC-NIRS)



➢ **Enhancement of the effect of high energy photons and fast ions**

Salado-Leza D et al. Nanotechnology, science and applications (2020).

Quantification of molecular scale effects ?

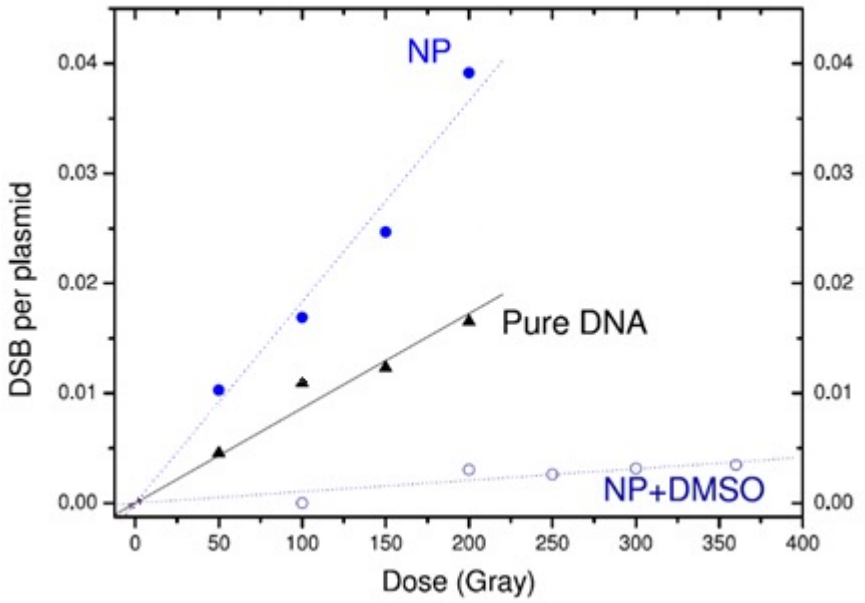


Quantification of nano-size damages (for simulations)

molecular probe : DNA plasmids

pBr322 plasmid = Nano-biodosimeter

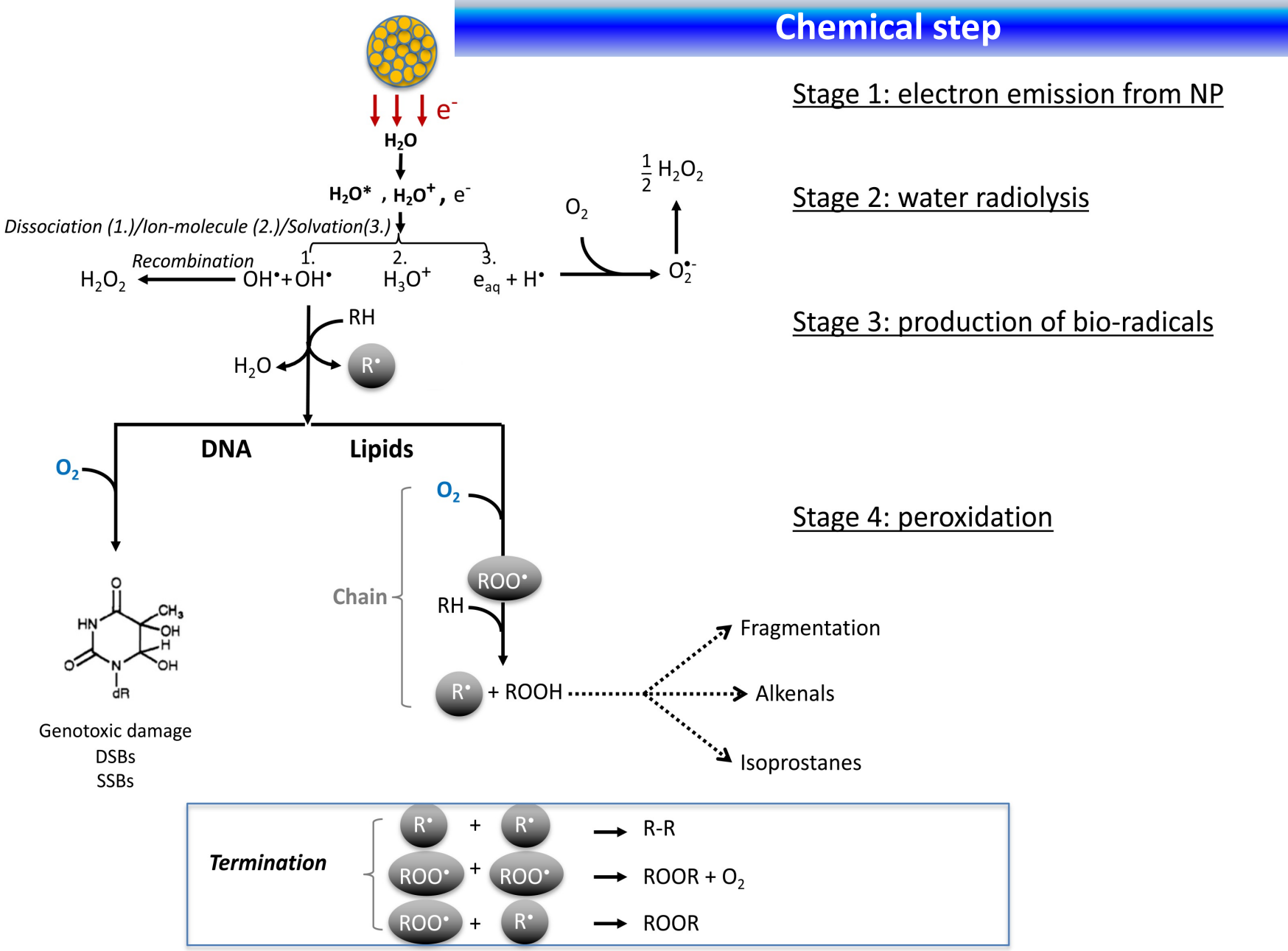
Double strand break (DSB)
> 2 nm damage



- Enhancement of lethal radiation effects (nanosize damage)
- Major role of water radicals

Porcel et al Nanotechnology 21, 85103 (2010) *Salado-Leza D et al. Nanotech science and appli. (2020).*

Chemical step



Stage 1: electron emission from NP

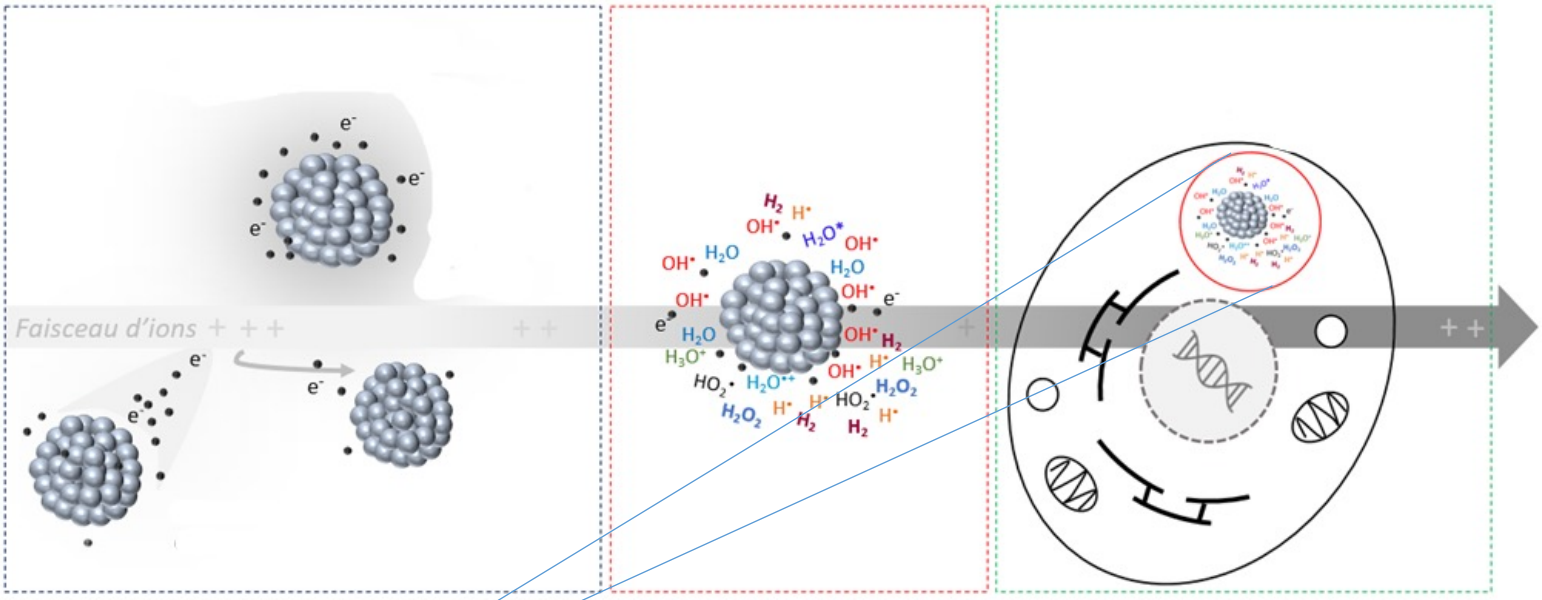
Stage 2: water radiolysis

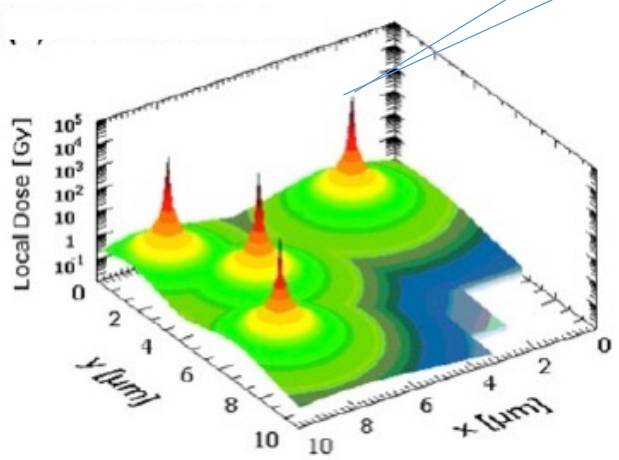
Stage 3: production of bio-radicals

Stage 4: peroxidation

1. *J. Schuemann et al Phys Med Biol 2020 DOI: 10.1088/1361-6560/ab9159.*

Prediction / simulations: nanoscale mechanisms





Effect of NPs at nanoscale:

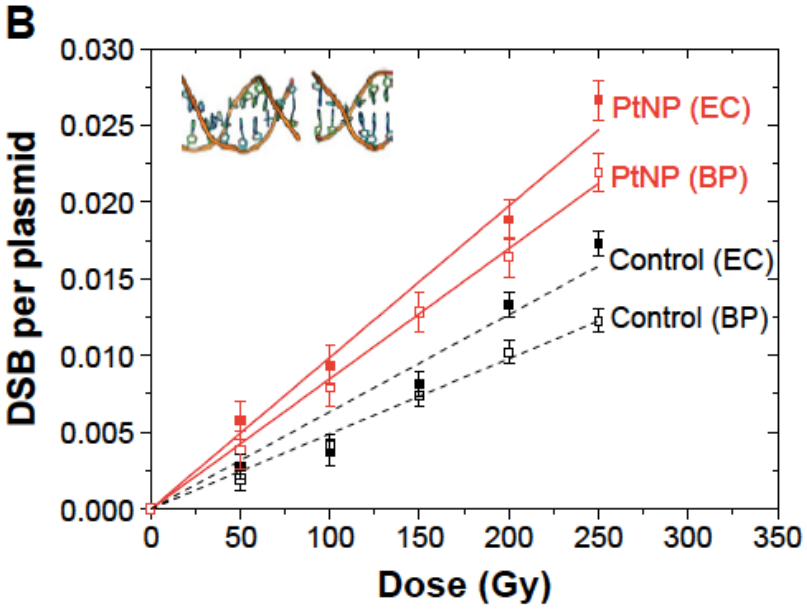
- Confined nanodose deposition (« spikes »)
- Able to induce nano-size damage

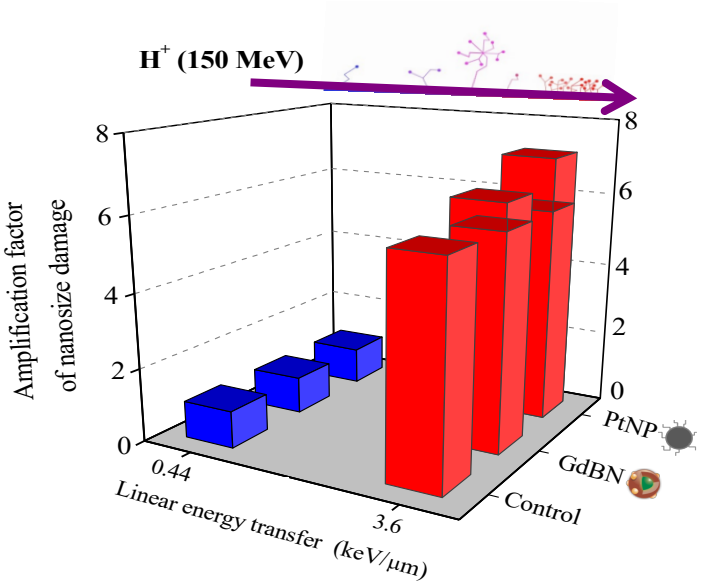
in biomolecules

- Cell death and other biological impacts

Mc Mahon et al Scientific Reports (2011)

PtNPs @ 150 MeV protons.





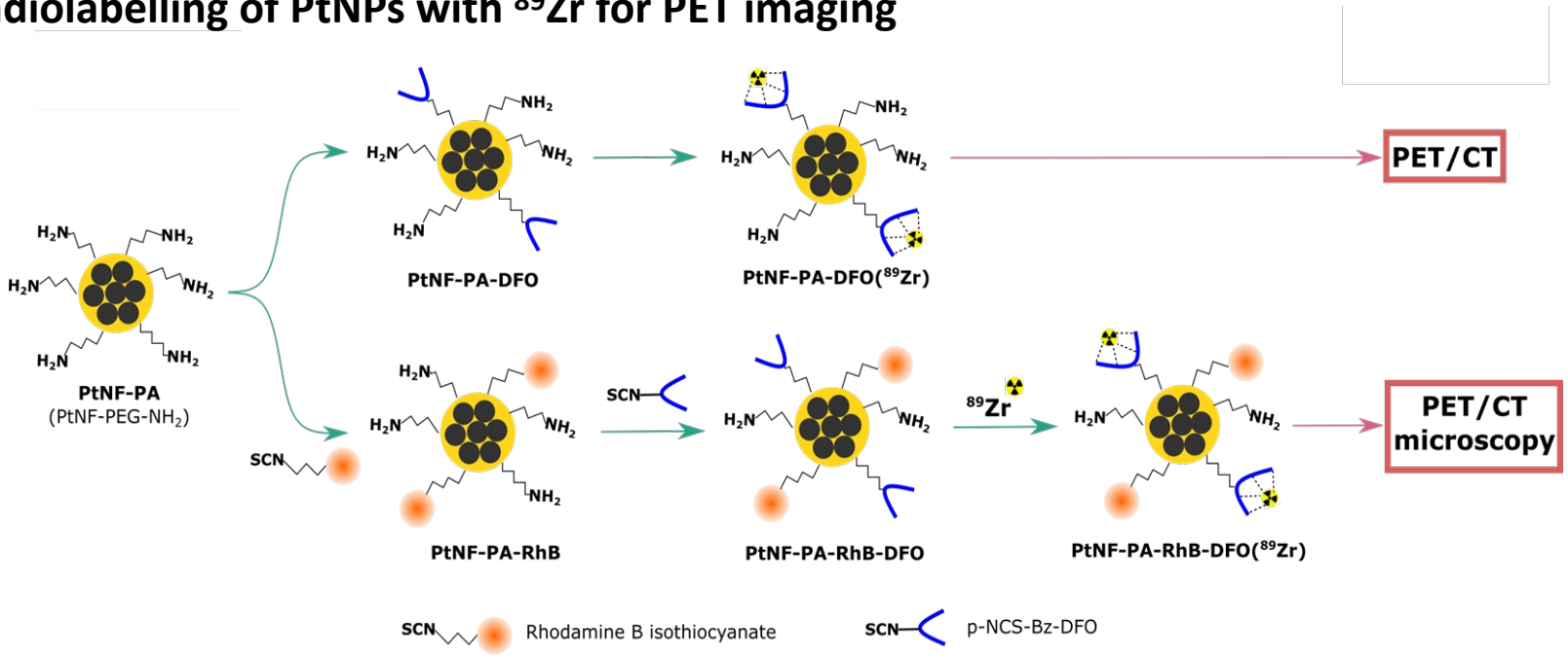
- Effect **stronger at the end** of the proton track
- Increase of the effect with higher Z

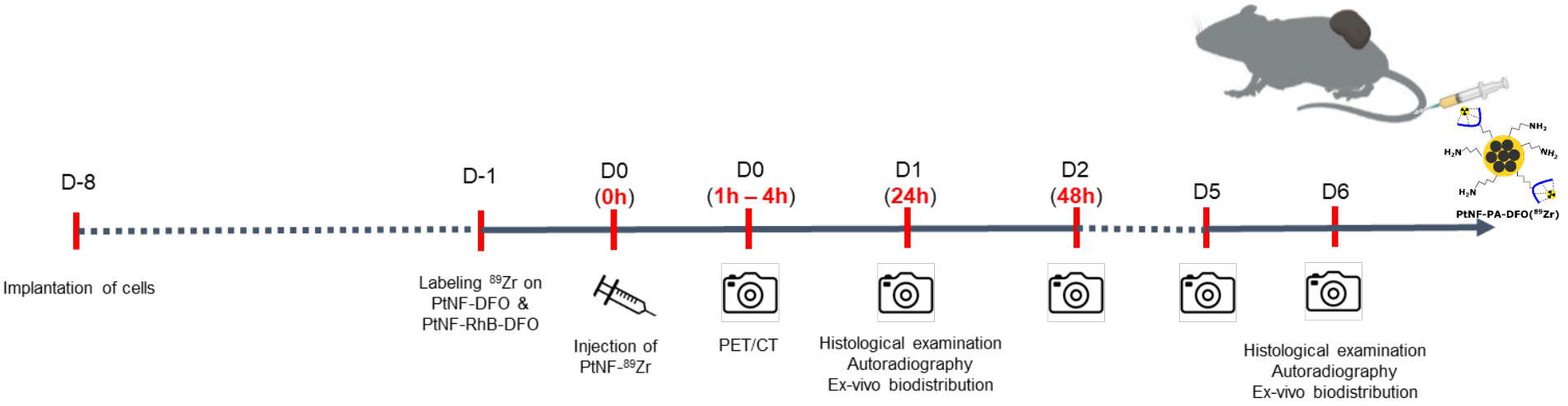
Schlathölter et al, Int. J. Nanomed. (2016)

in vivo

PtNP pharmacokinetic and biodistribution

Radiolabelling of PtNPs with ^{89}Zr for PET imaging

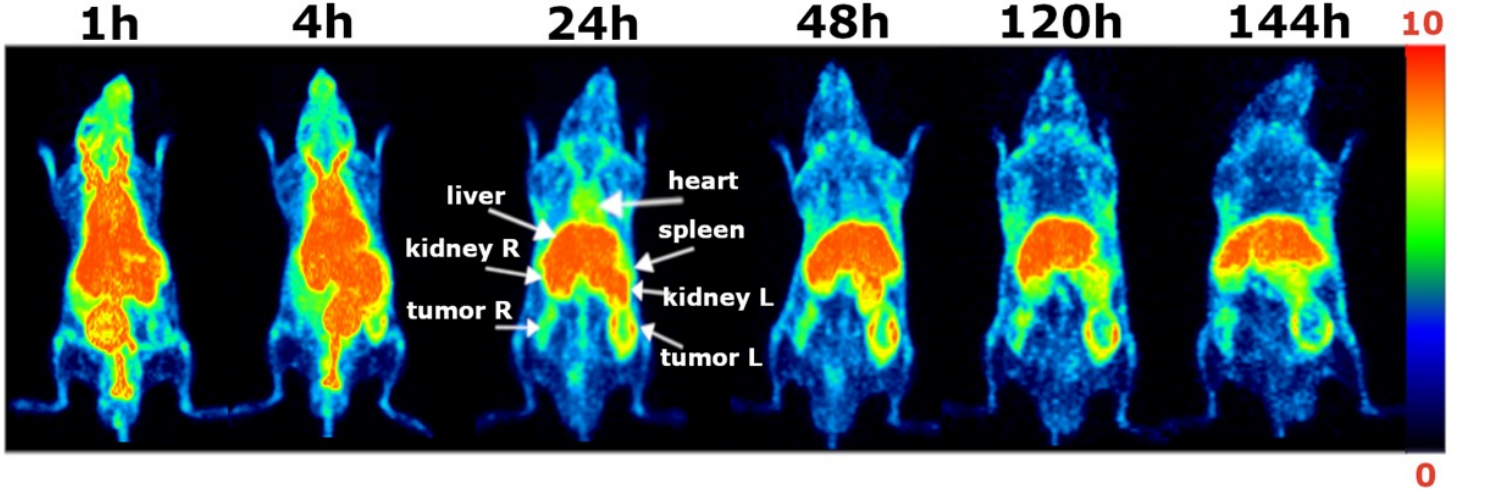




Yang et al, Nanomedicine NMB (2022)

NP pharmacokinetic and biodistribution of PtNP

In vivo Biodistribution of ^{89}Zr-PtNP in B16F10 tumor model



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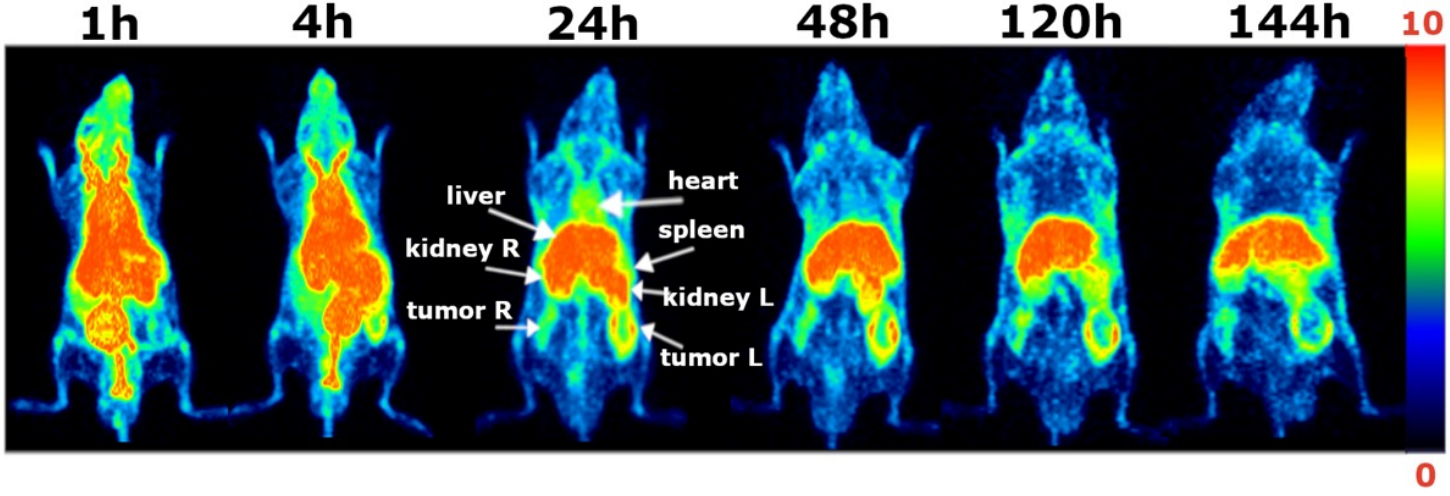

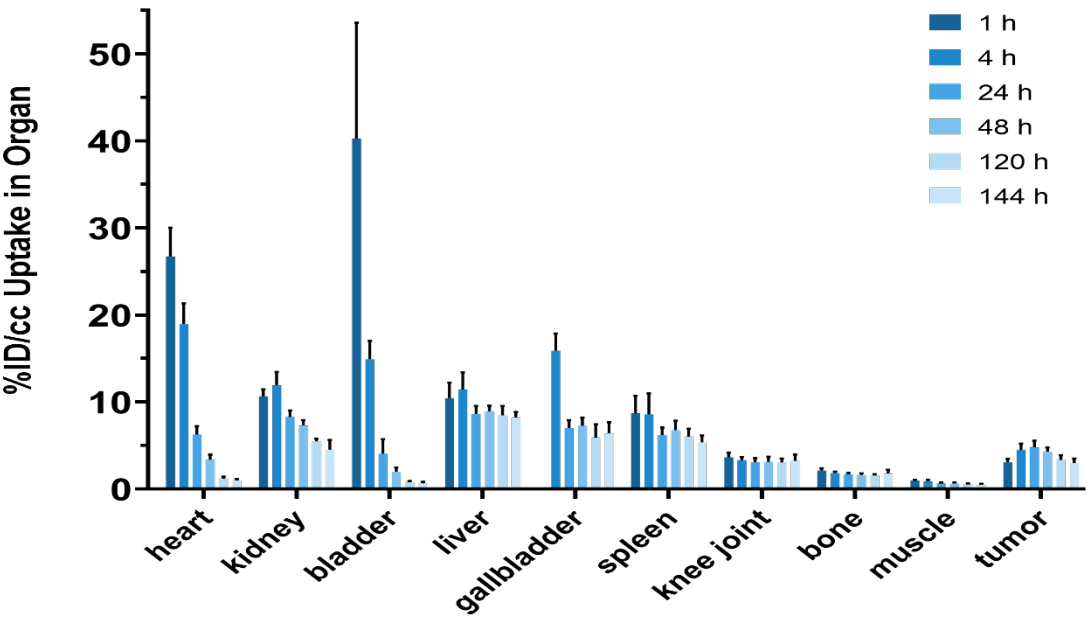

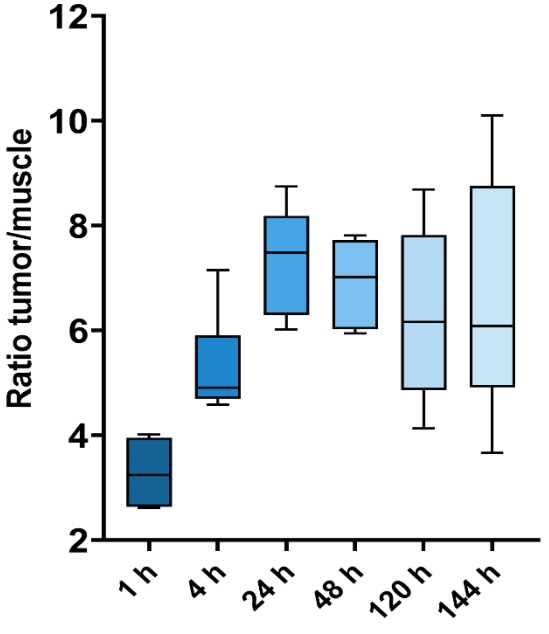

Yang et al, Nanomedicine NMB (2022)

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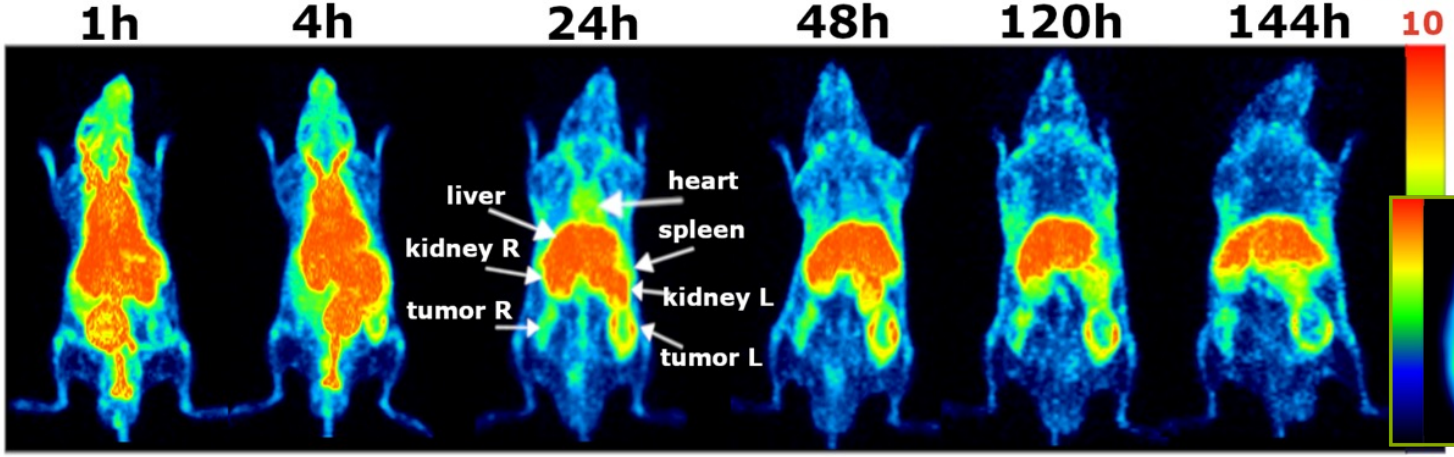
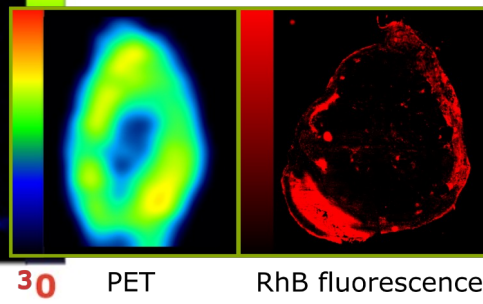
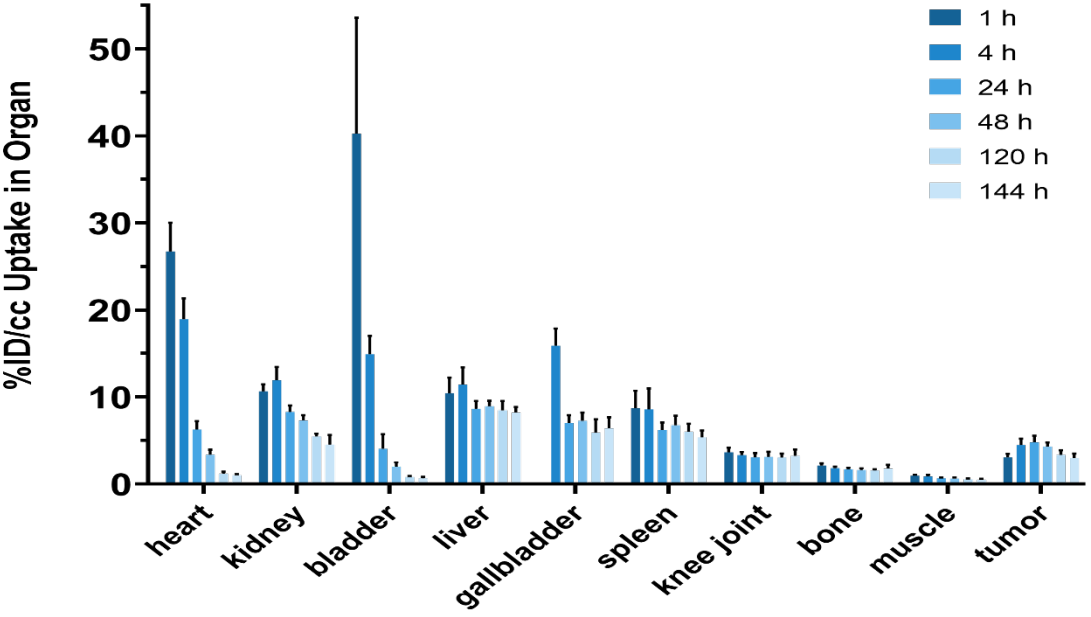
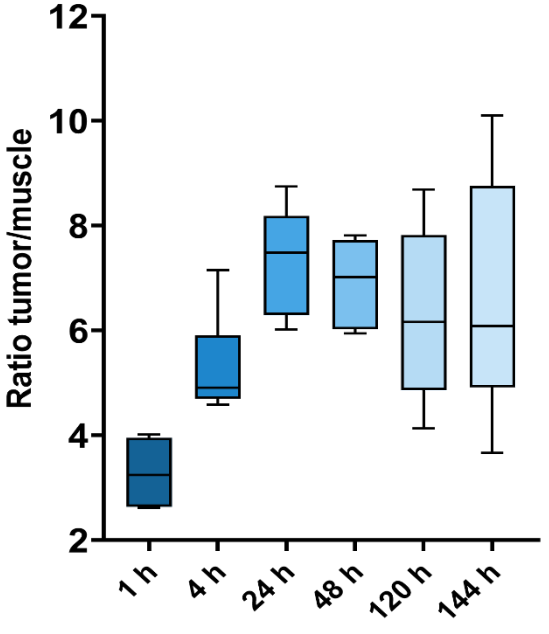


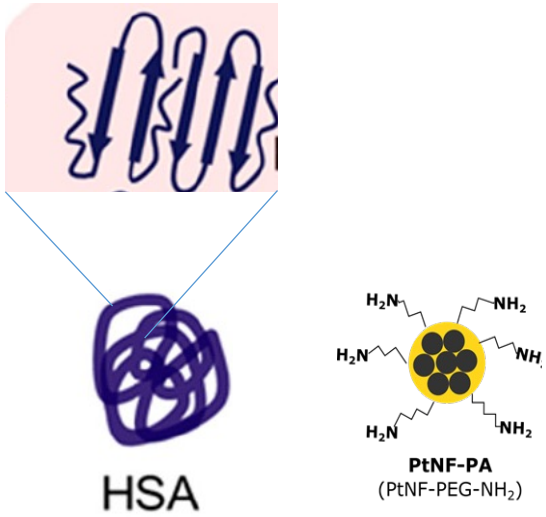






Yang et al, Nanomedicine NMB (2022)

Interaction of PtNPs with blood proteins



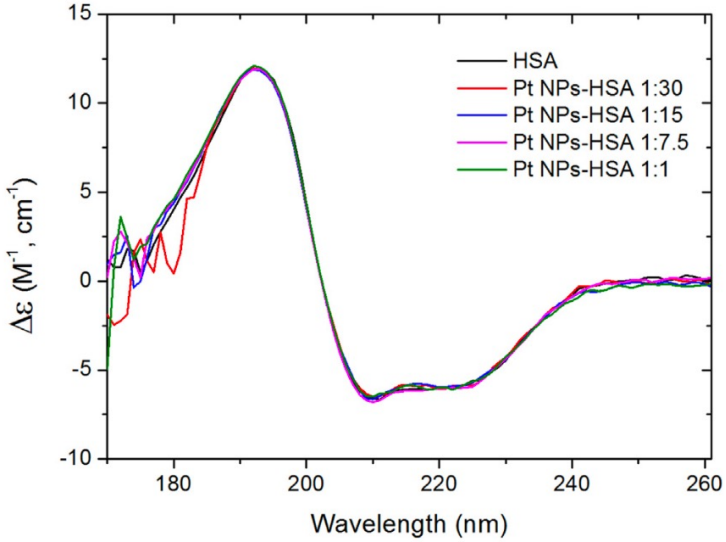


Figure 5. SRCD spectra of HSA alone and Pt NPs-HSA complex at Pt NPs:HSA molar ratios of 1:30, 1:15 and 1:7.5 and 1:1, respectively at pH=7.4, 37 °C.

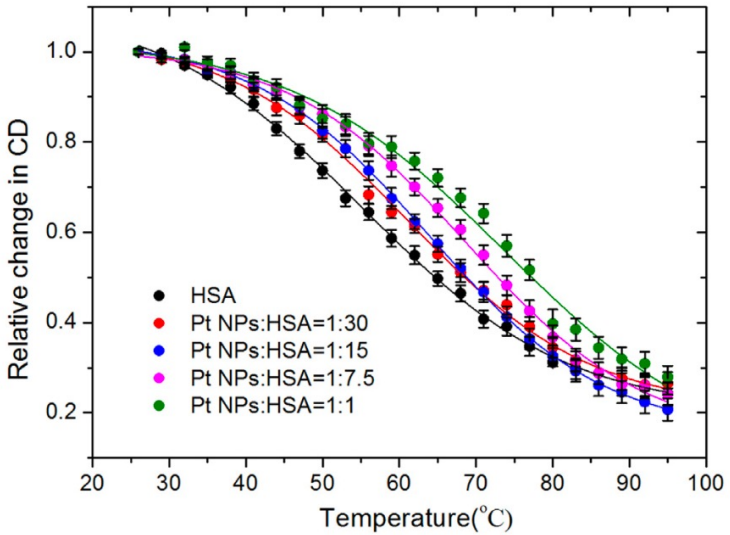


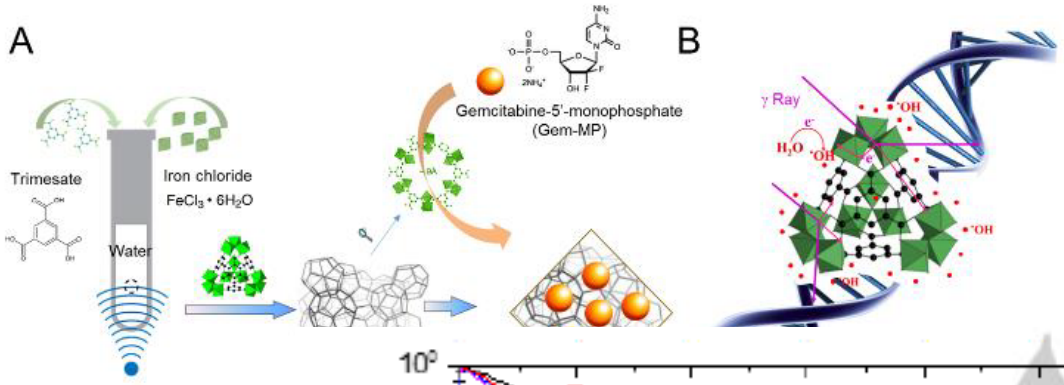
Figure 7. Thermal denaturation curves of pure HSA and the Pt NPs-HSA complex at different ratios (Pt NPs:HSA = 1:30, 1:15, 1:7.5, and 1:1) monitored at 192 nm.

- No interaction of NPs with blood proteins (CD)
- but light interaction at high concentration of 1:1 (temperature scan)

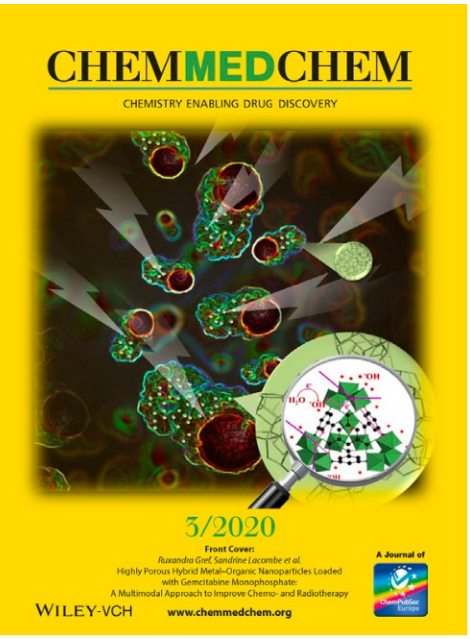
Yang et al. J. Pharmaceutical Sc. 2024

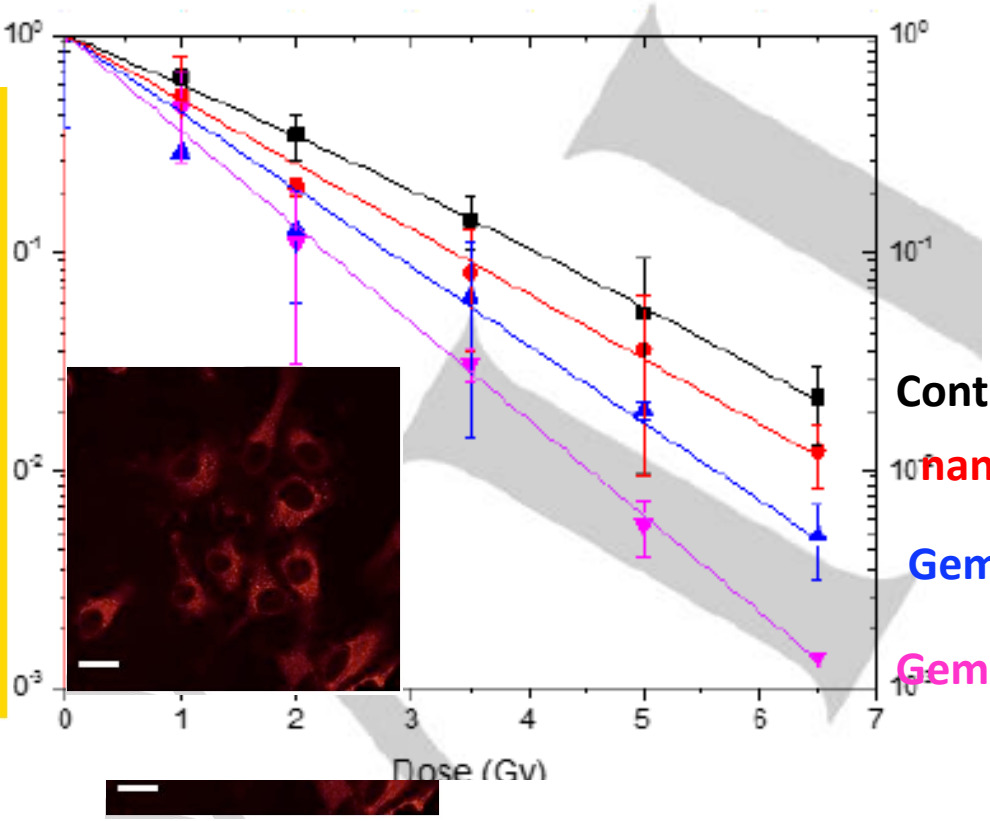
Towards personalized treatments

NanoMOFs (Metal Organic Framework) loaded with Gemcitabine



Radioenhancer (Fe)
+ transporter of Gem (radiosensitizer)





Control

nanoMOFs

Gem-MP

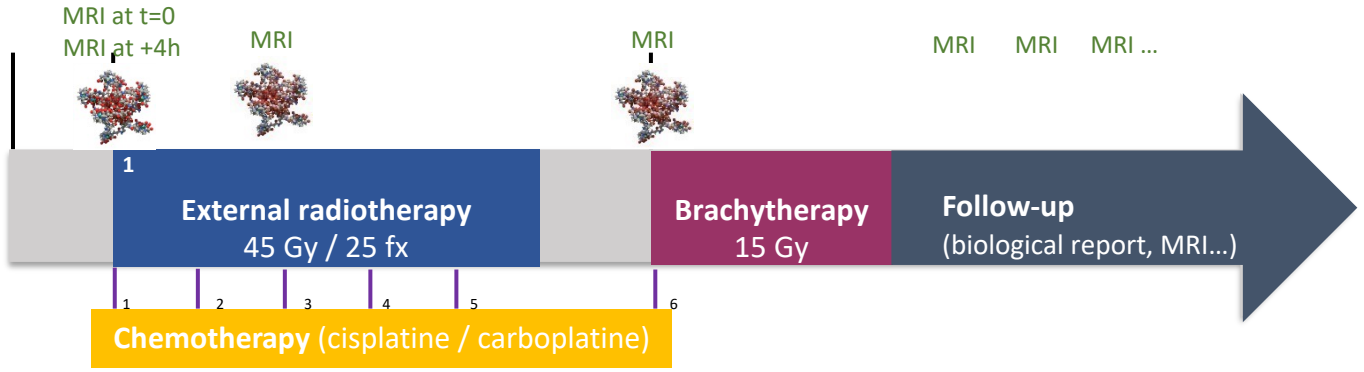
Gem-MP loaded nanoMOFs

Li et al ChemMedChem 2020

Theranostic : NP quantification in tumors and RT

Nanocol: Phase I clinical trial -advanced cervical cancers

- IV injections of Gd based NPs (AGuiX)
- MRI follow-up and NP quantification
- RT & brachytherapy



Maury et al Front. Bioeng. Biotechnol., 2021

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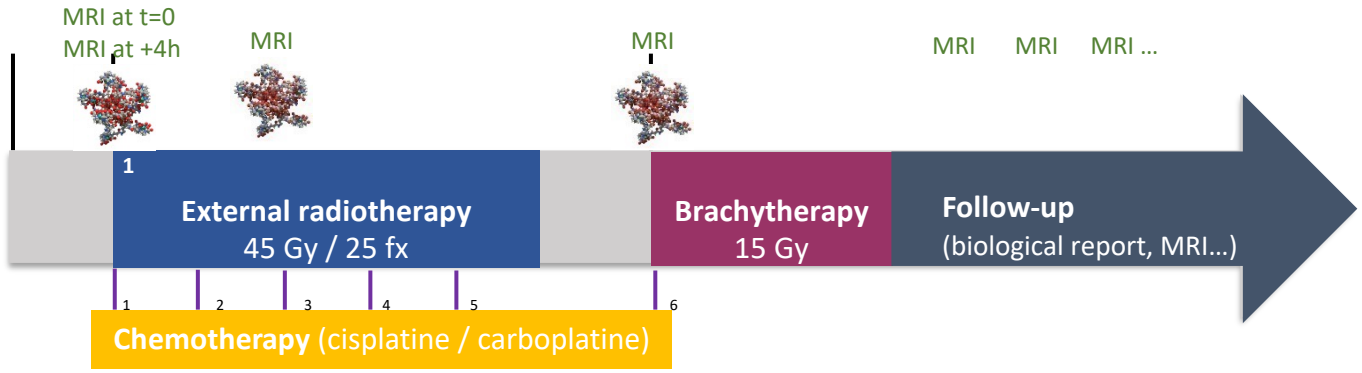


In parallel : in vitro evaluation of radioenhancement effect

AGuiX in cells (2D & organoids) + radiation effects

➢ **Prediction of radioenhancement for each patient based on MRI images**

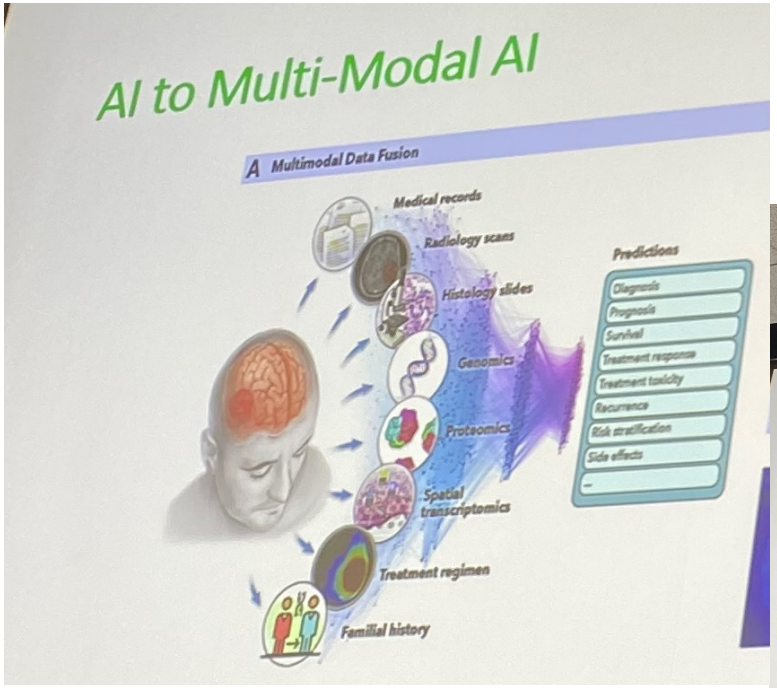
Maury et al Front. Bioeng. Biotechnol., 2021

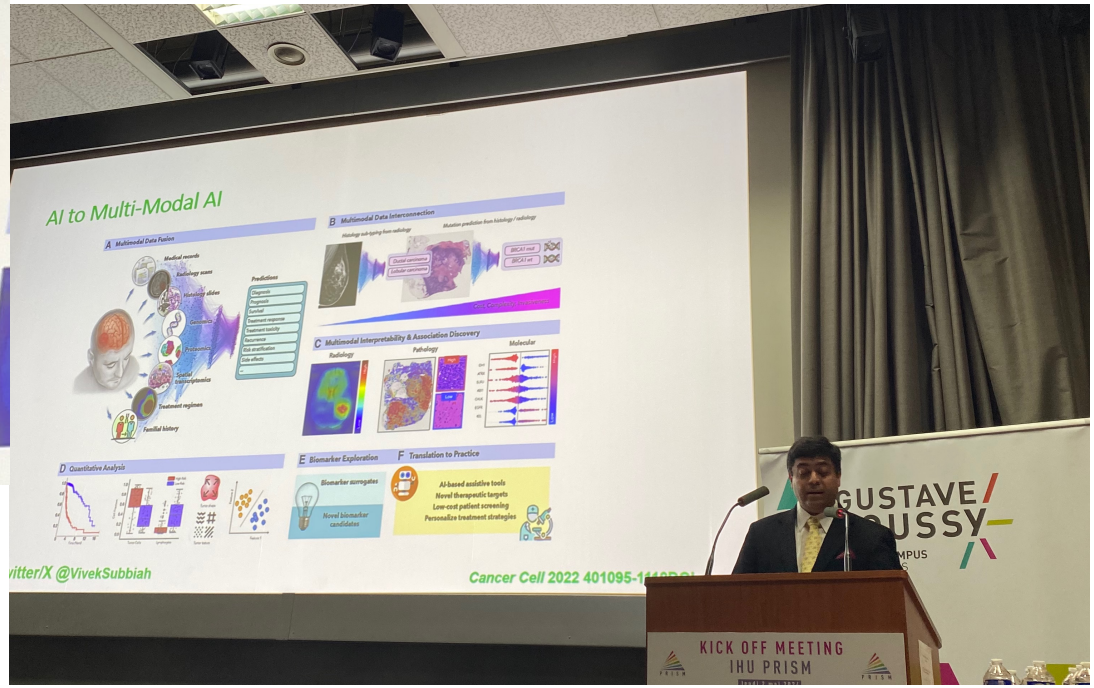
Perspectives

Perspectives: multimodal AI for personalized medicine

« A Vision of patient-centric precision medicine 2030 »
(Talk Inst. Gustave Roussy, U. Paris Saclay, 2024)

Individualization of treatments based on genetic & molecular characteristics rather



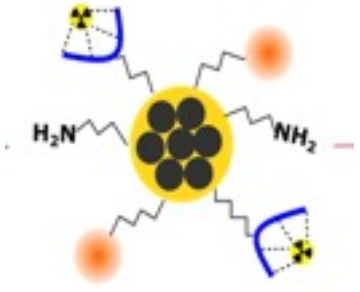


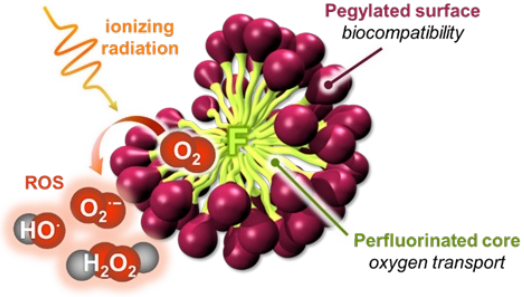
V. Subbiah, MD, Chief, Early phase development,
Sarah Cannon Research Institute, Nashville, US

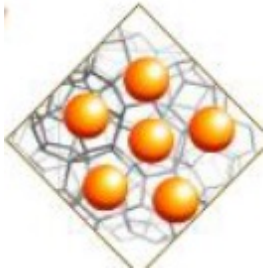
Summary & perspectives

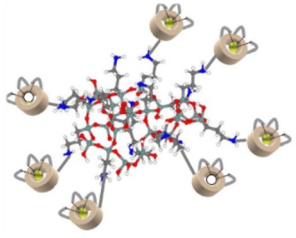
Where we are:

- ✓ **NP-driven theranostic strategies already in clinic**
- ✓ **New NPs in progress** but:
  - Need more NPs to improve tumor targeting and clearance, and offer a large panel of properties to physicians/med phys.,
  - Need new IT models and tools (simulations, AI..)
    - Multidisplinary collaborations with chemists
- ✓ Some spin-off but need of higher interest of **big pharma** and other **industrials**









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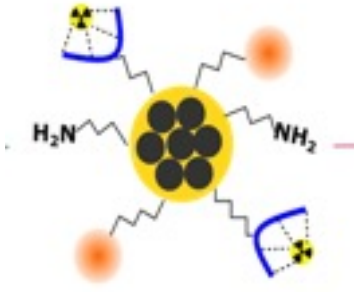
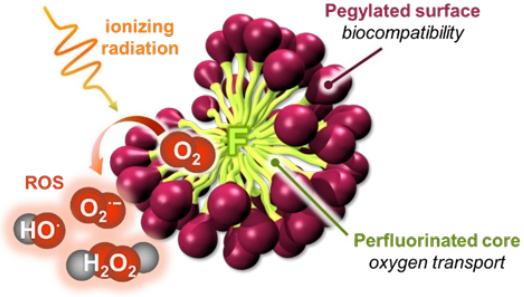
What's next :

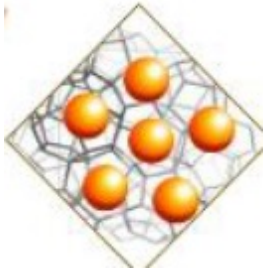
Effect of NPs with new radiation modalities (UHDR/FLASH, microbeams etc)

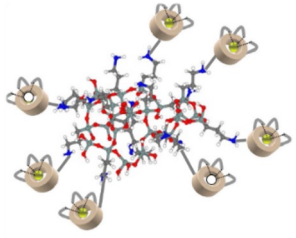
Clinical trials with new NPs

Development of models/simulations/AI to predict, control and personalize

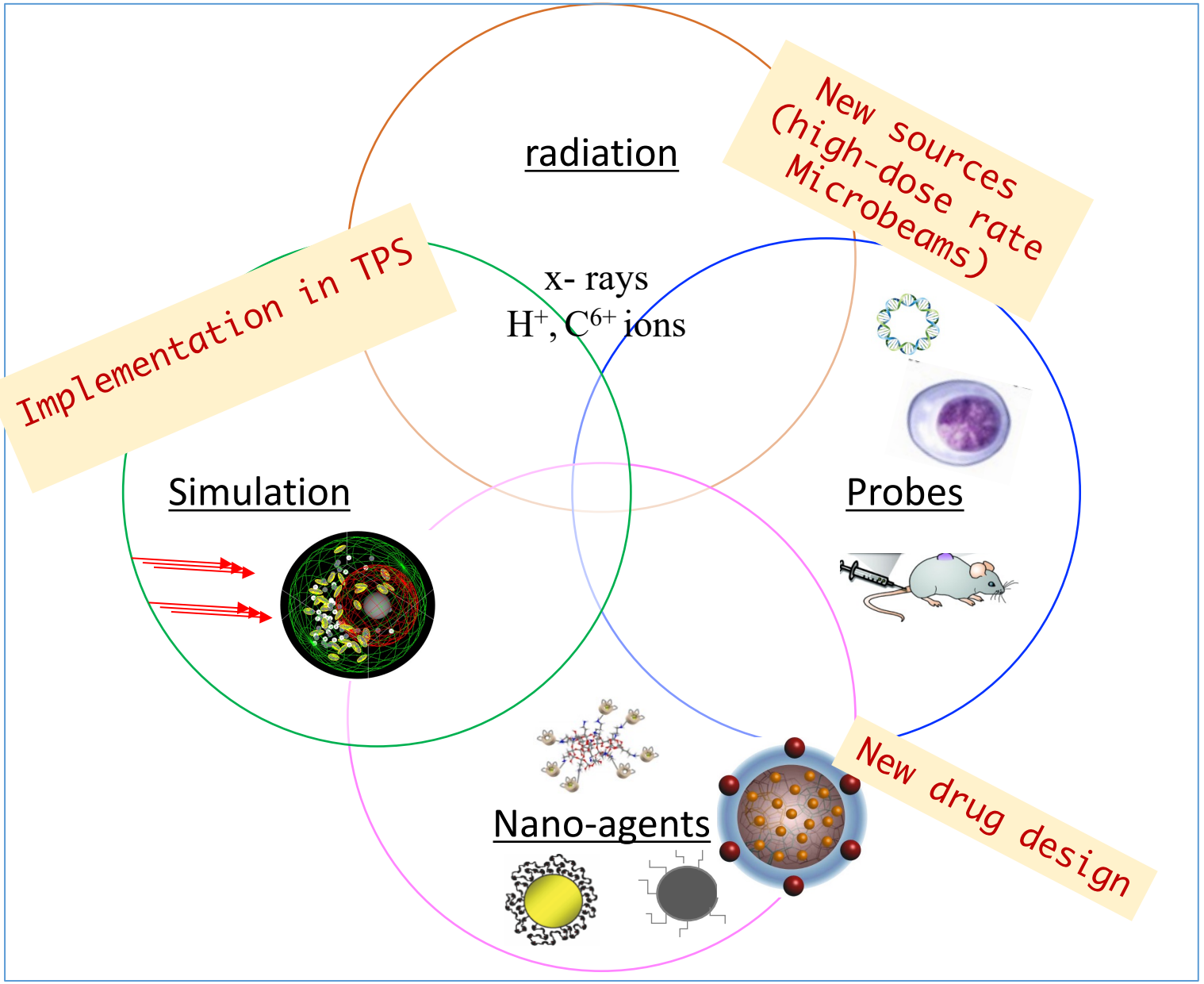








CHALLENGES



From fundamental
to
the clinic

MANY
OPPORTUNITIES

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