KILLING CANCER CELLS THROUGH CERENKOV-INDUCED PHOTODYNAMIC EFFECT

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Clinical Context

Glioblastoma (GBM)

- Grade IV astrocytoma

→ Infiltrative and invasive cancer cells

→ Most fast-growing and aggressive brain tumor

- 2400 cases/year in France

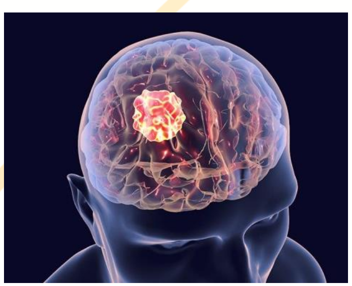
- Median age: 64 years


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D.,Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*



Current standard treatment

- ***Stupp* protocole**
  - ✓ Tumor resection
  - ✓ + Chemotherapy (Temozolomide)
  - ✓ + External radiotherapy (X ray → 60 Gy)

→ < 5 year-GBM survival rate is only for 6.8% patients

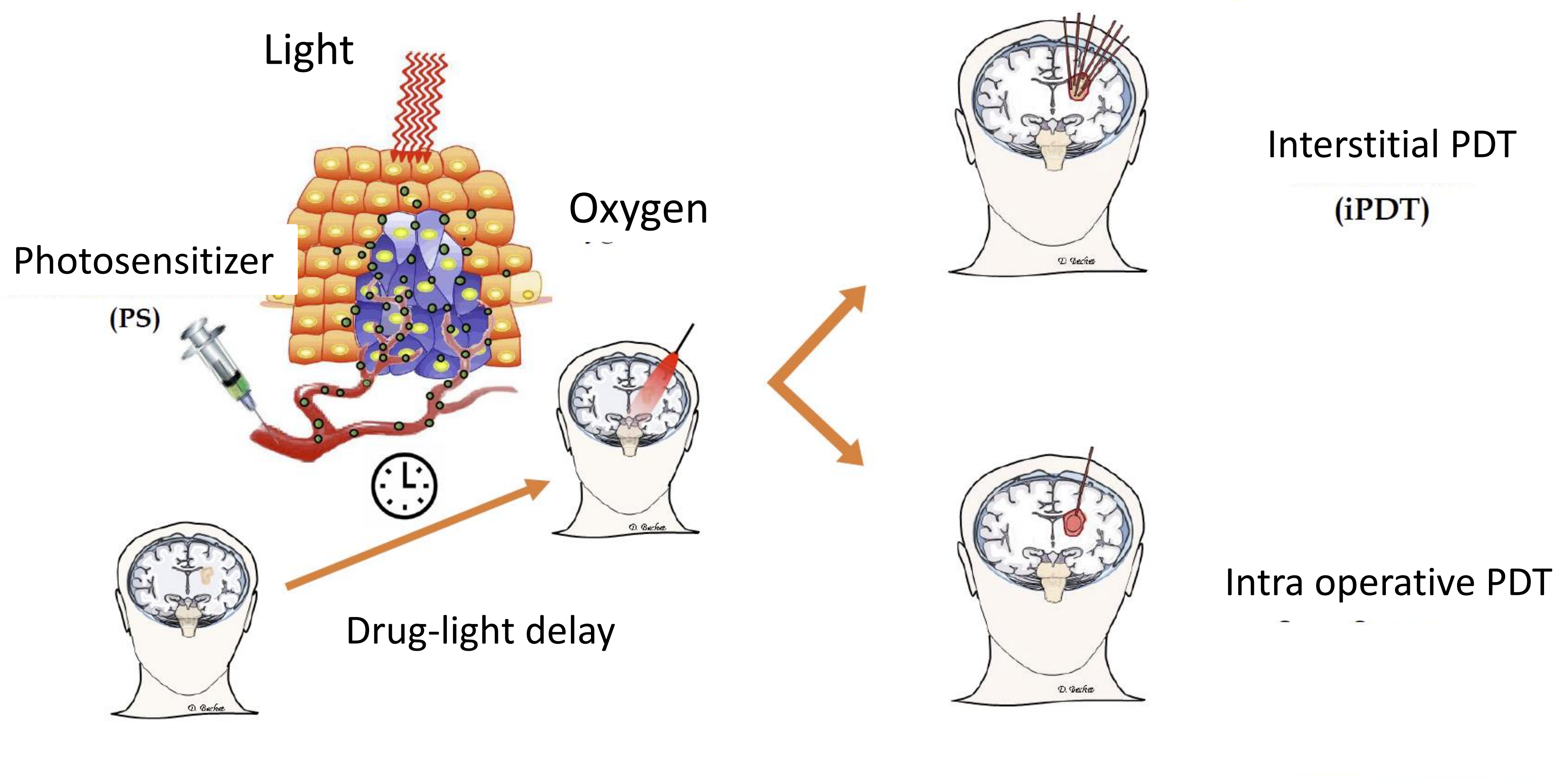
→ Alternative ?

→ Photodynamic therapy (PDT)

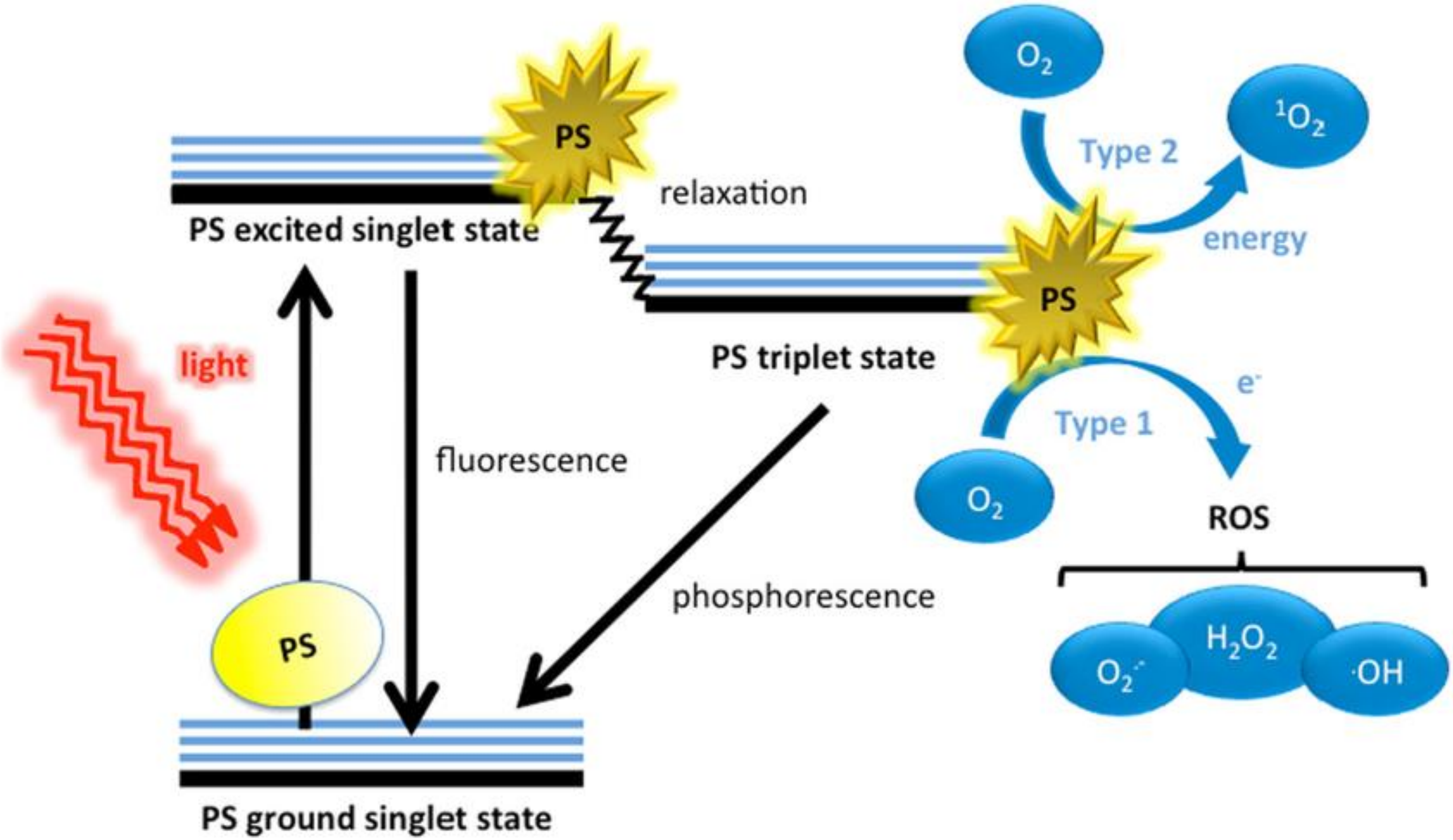
Low light penetration depth is the main limiting point

Poor tissue penetration

PHOTODYNAMIC THERAPY

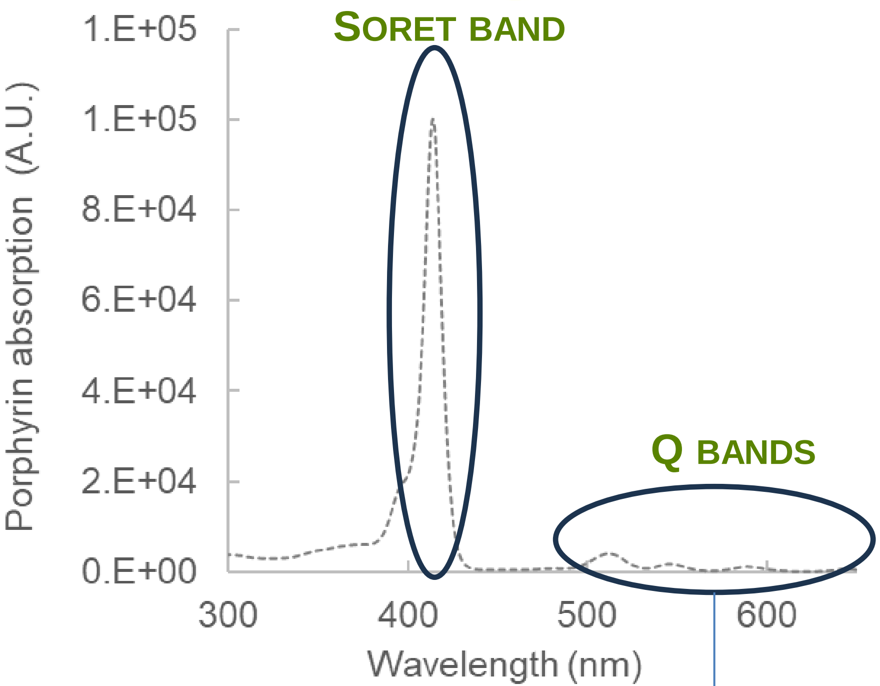


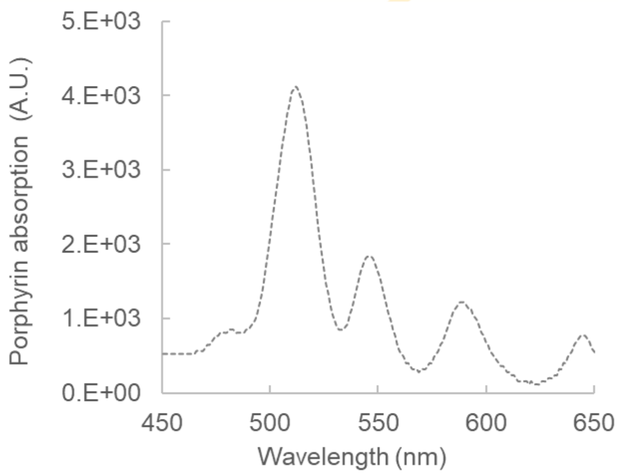
PHOTODYNAMIC THERAPY
JABLONSKI DIAGRAM



PHOTODYNAMIC THERAPY PRINCIPLE

- **Photosensitizer properties**
  - Non cytotoxic without light
  - High singlet oxygen quantum yield
  - Large spectral overlap with light source





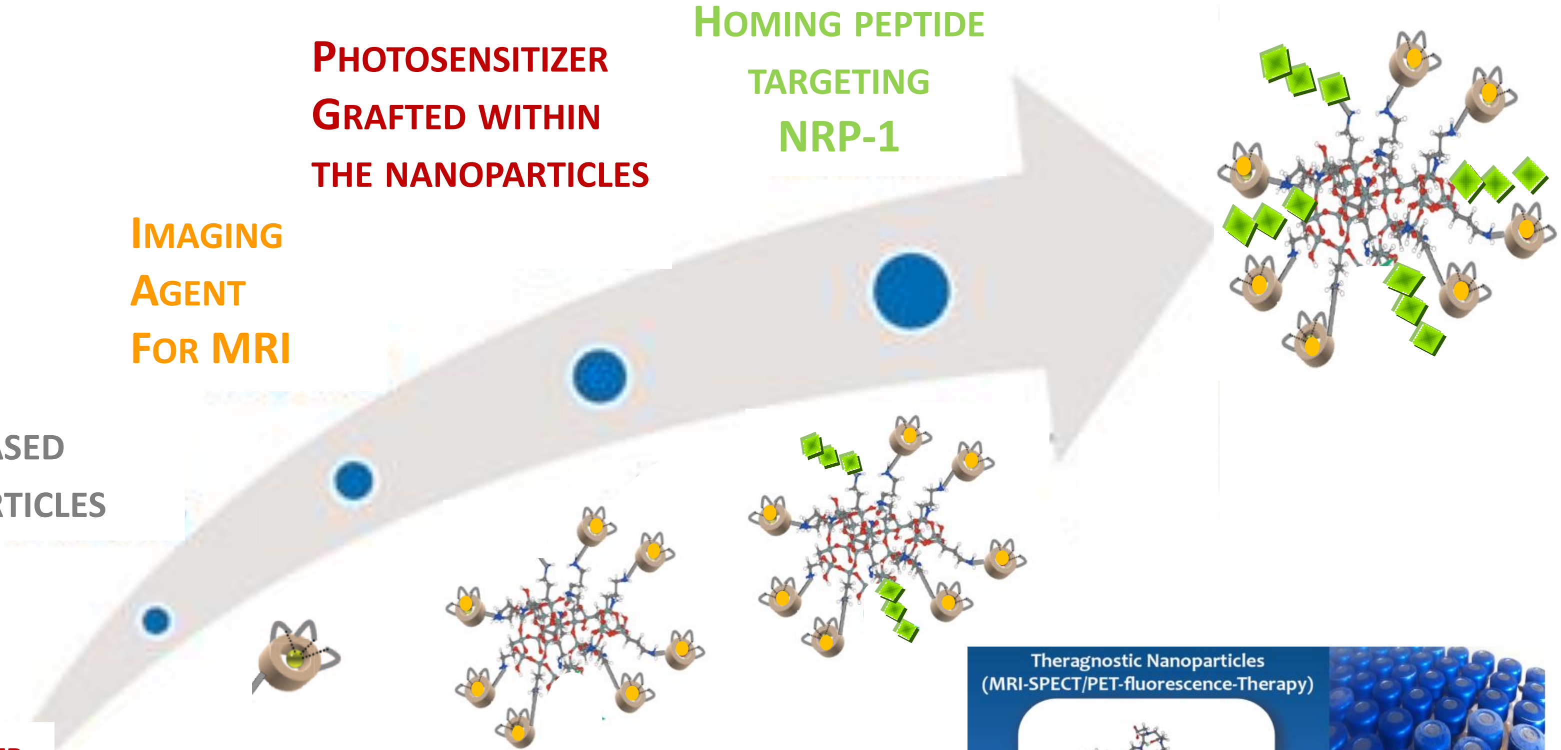
PHOTODYNAMIC THERAPY: CLINICALLY FEASIBLE

INDYGO

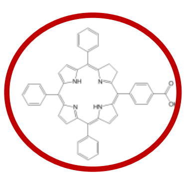
Etude de Phase 1 de thérapie photodynamique peropératoire du glioblastome

Sponsor de l'étude : CHU de Lille

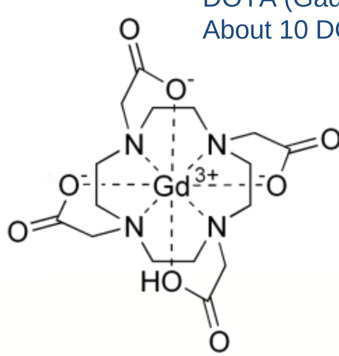
Objectif principal : Evaluer la faisabilité de la réalisation de la PDT per opératoire au cours de la chirurgie d'exérèse du glioblastome, sans toxicité immédiate inacceptable.

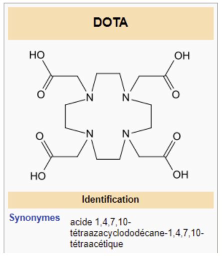


Photosensitizer



DOTA (Gadolinum chélaté)
About 10 DOTAs/nanoparticle

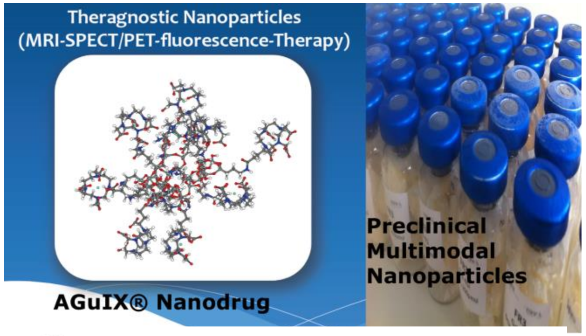




DOTA

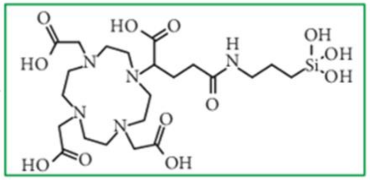
Identification

Synonymes: acide 1,4,7,10-tétraazacyclododécane-1,4,7,10-tétraacétique

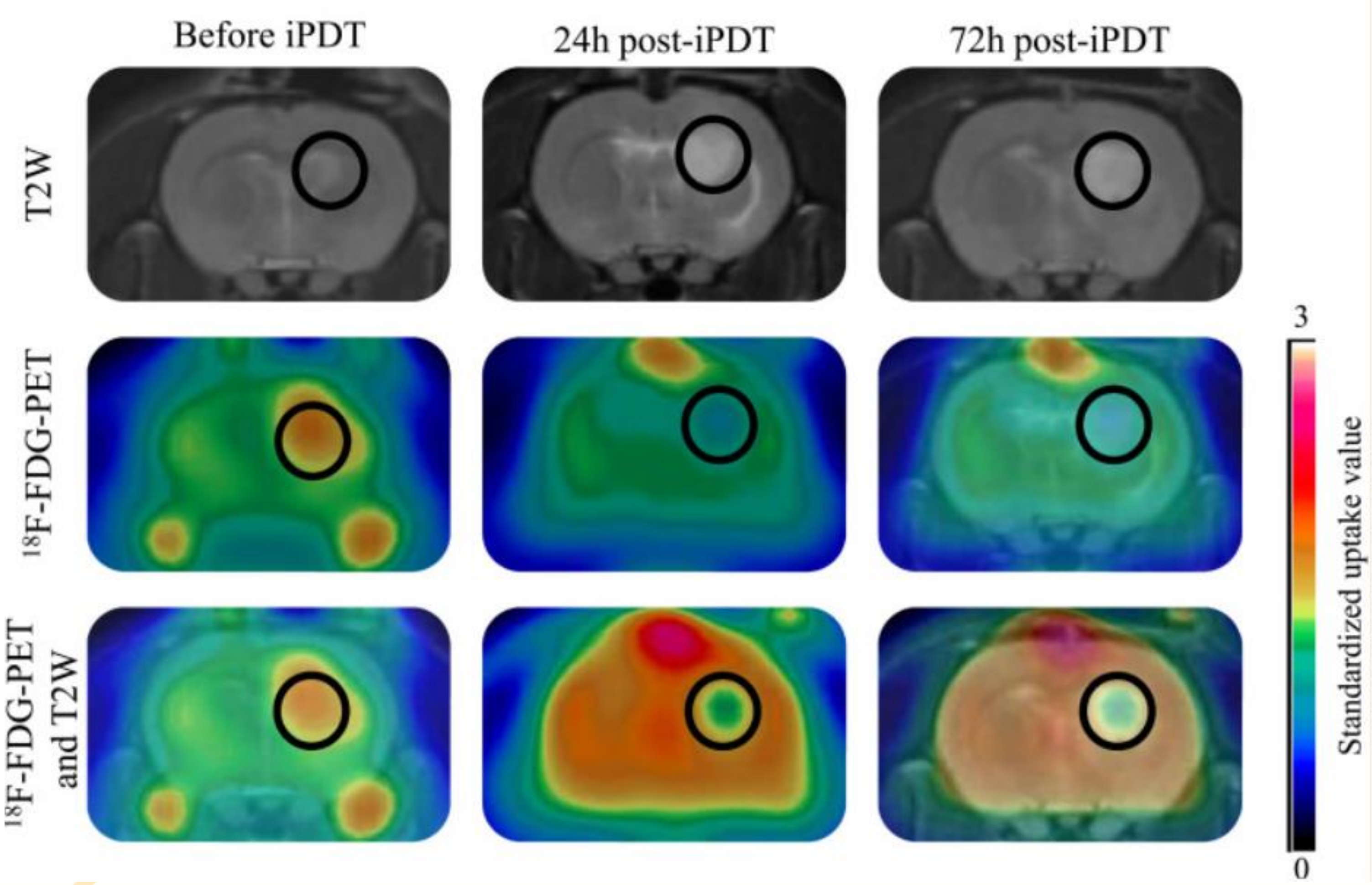


CheMatech macrocycle design technologies

nano-h Value-Added Nanotechnology

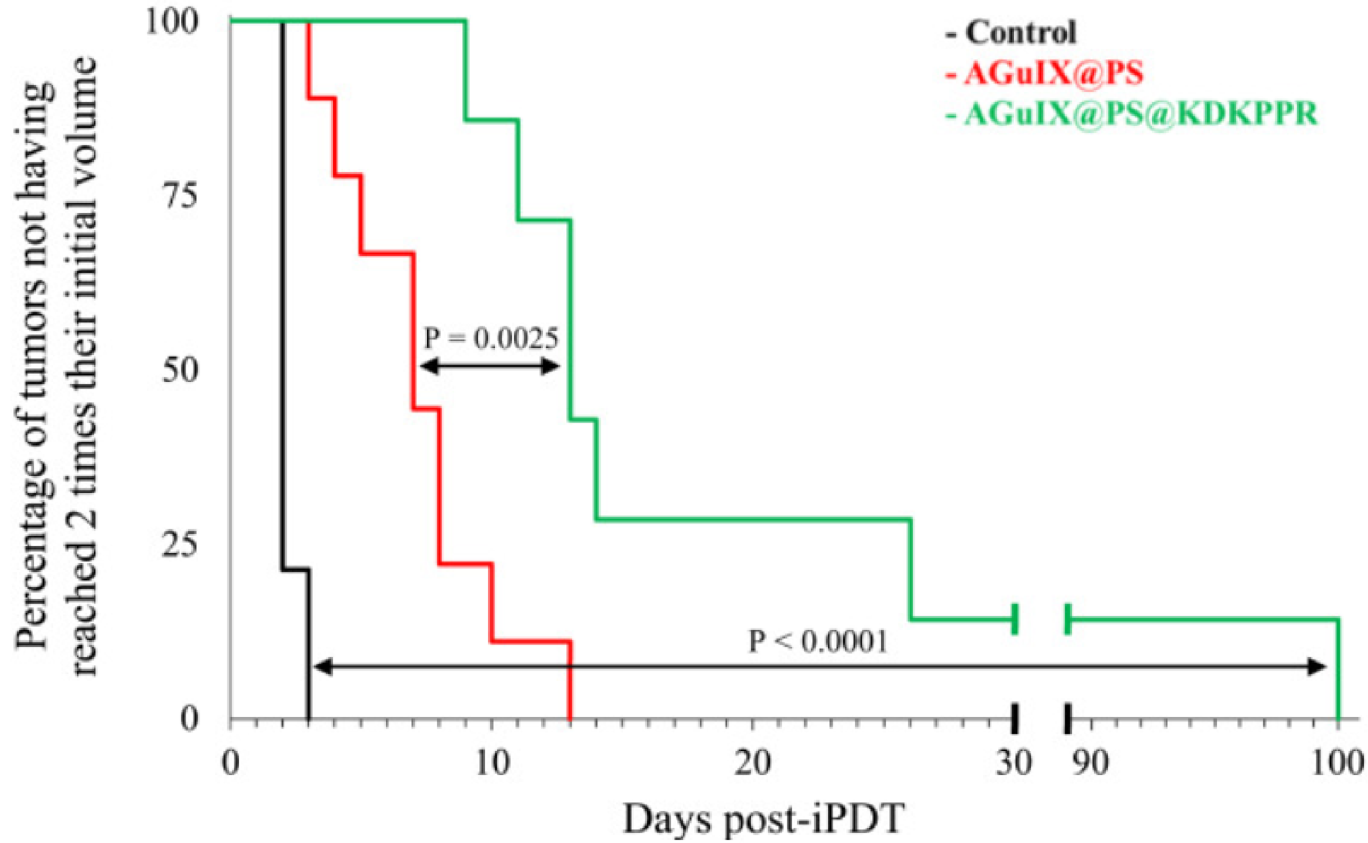


PHOTODYNAMIC THERAPY PRINCIPLE



652 nm, 26 J, 8min
Only 1 session

PHOTODYNAMIC THERAPY PRINCIPLE



International Journal of Nanomedicine

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ORIGINAL RESEARCH

Multiscale Selectivity and in vivo Biodistribution of NRP-1-Targeted Theranostic AGuIX Nanoparticles for PDT of Glioblastoma

Mickaël Gries[1]
Noémie Thomas[1]
Joël Daouk[1]
Paul Rocchi[2]

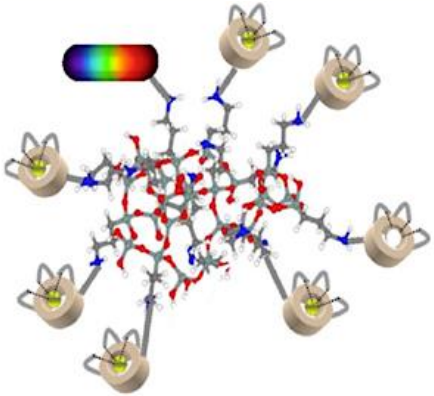
Background: Local recurrences of glioblastoma (GBM) after heavy standard treatments remain frequent and lead to a poor prognostic. Major challenges are the infiltrative part of the tumor tissue which is the ultimate cause of recurrence. The therapeutic arsenal faces the difficulty of eradicating this infiltrating part of the tumor tissue while increasing the targeting

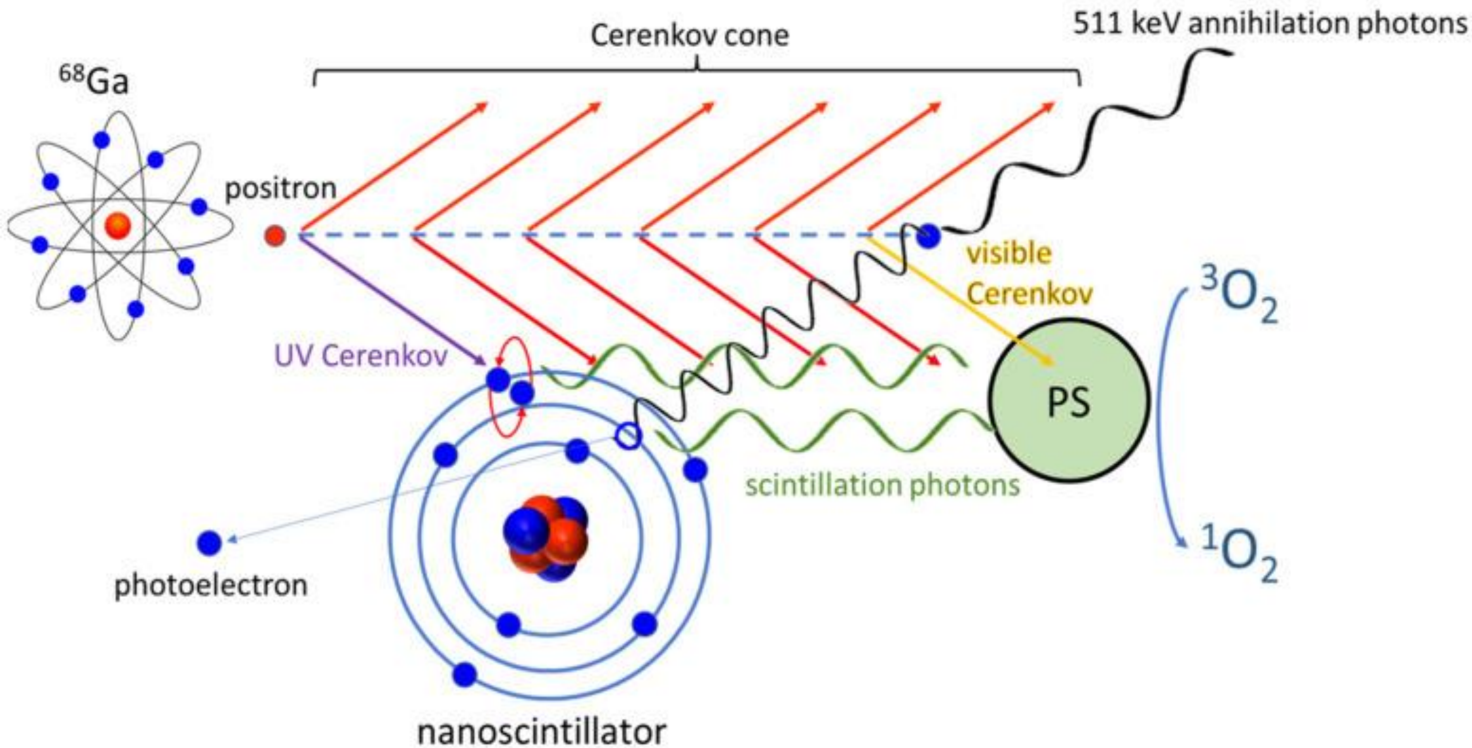
This article was published in the following Dove Press journal:
International Journal of Nanomedicine

BioSiS

Cerenkov-induced photodynamic therapy

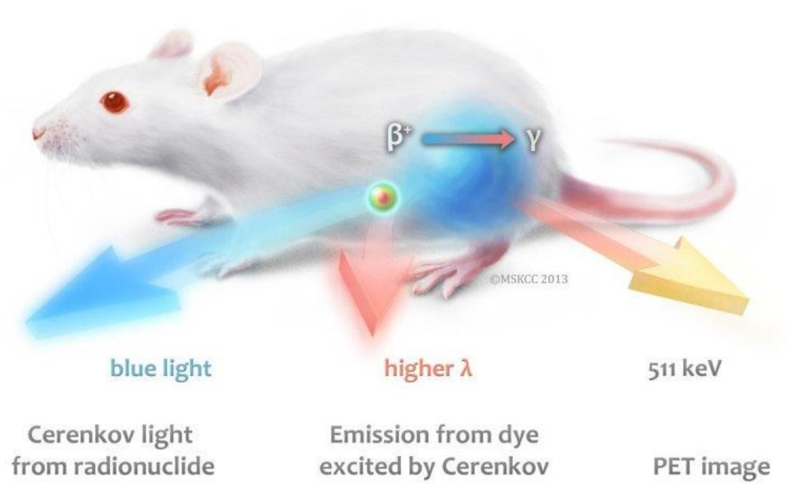
Nanoparticle interest:
- **Functionnalized AGuIX-derived**
- **Nanoscintillator chelates**





Schneller et al, Pharmaceuticals, 2023

CERENKOV-INDUCED PHOTODYNAMIC THERAPY



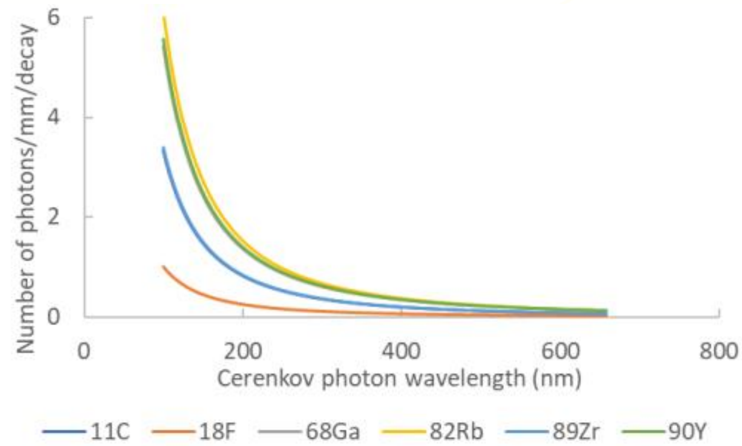
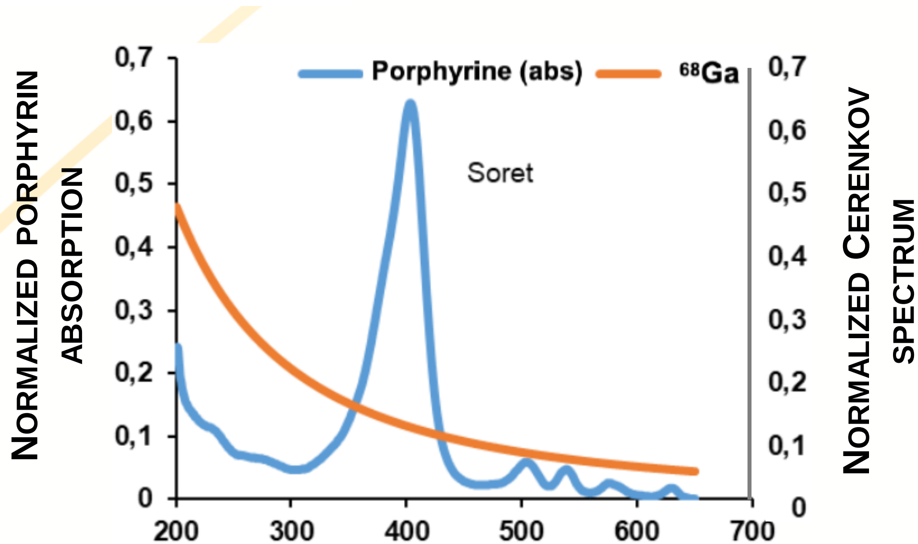
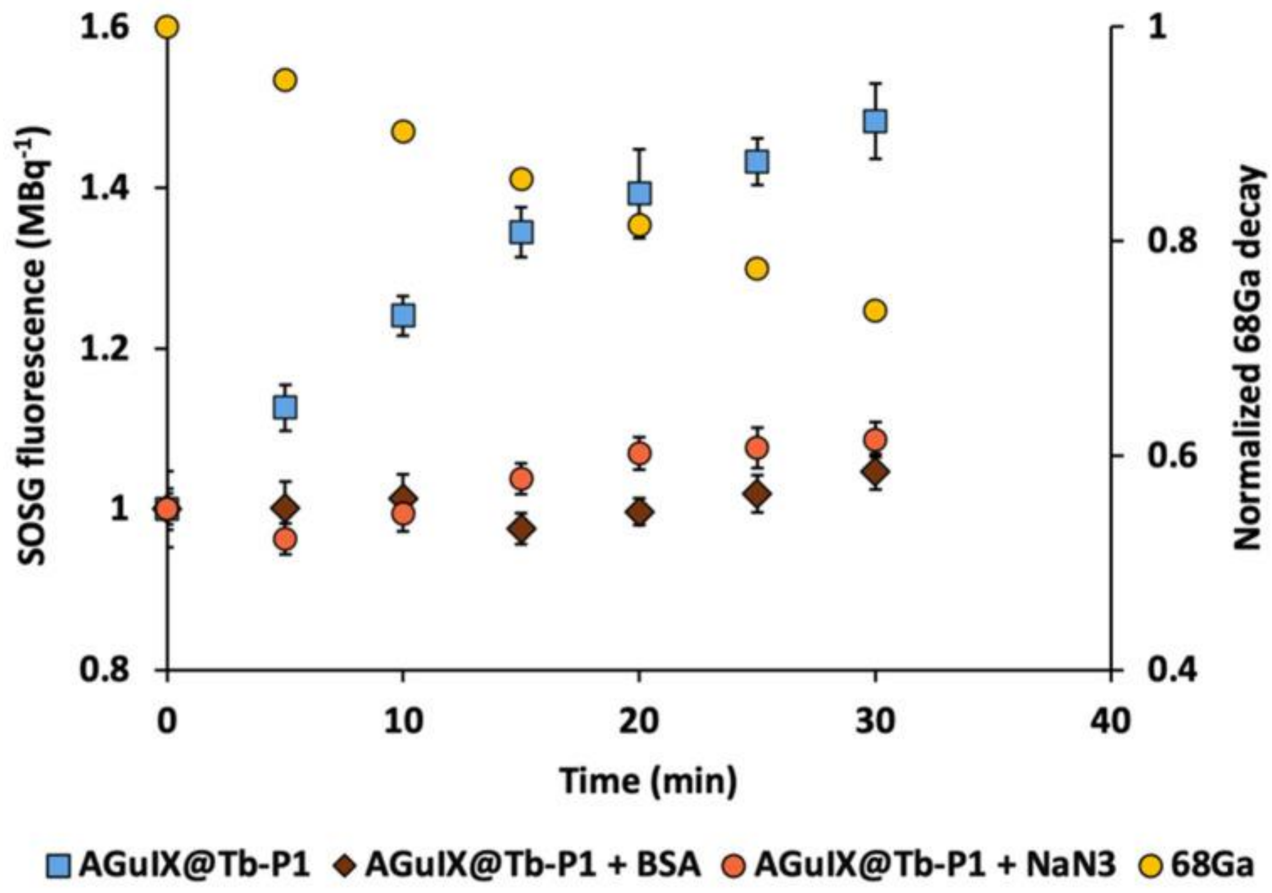


Figure 2. Cerenkov spectrum for ^{18}F, ^{68}Ga and ^{89}Zr decay in biological medium. Spectra were defined between 100 and 650 nm. To ease reading, number of photons are expressed relatively to ^{18}F at 100 nm.



Daouk et al, Radiation, 2020

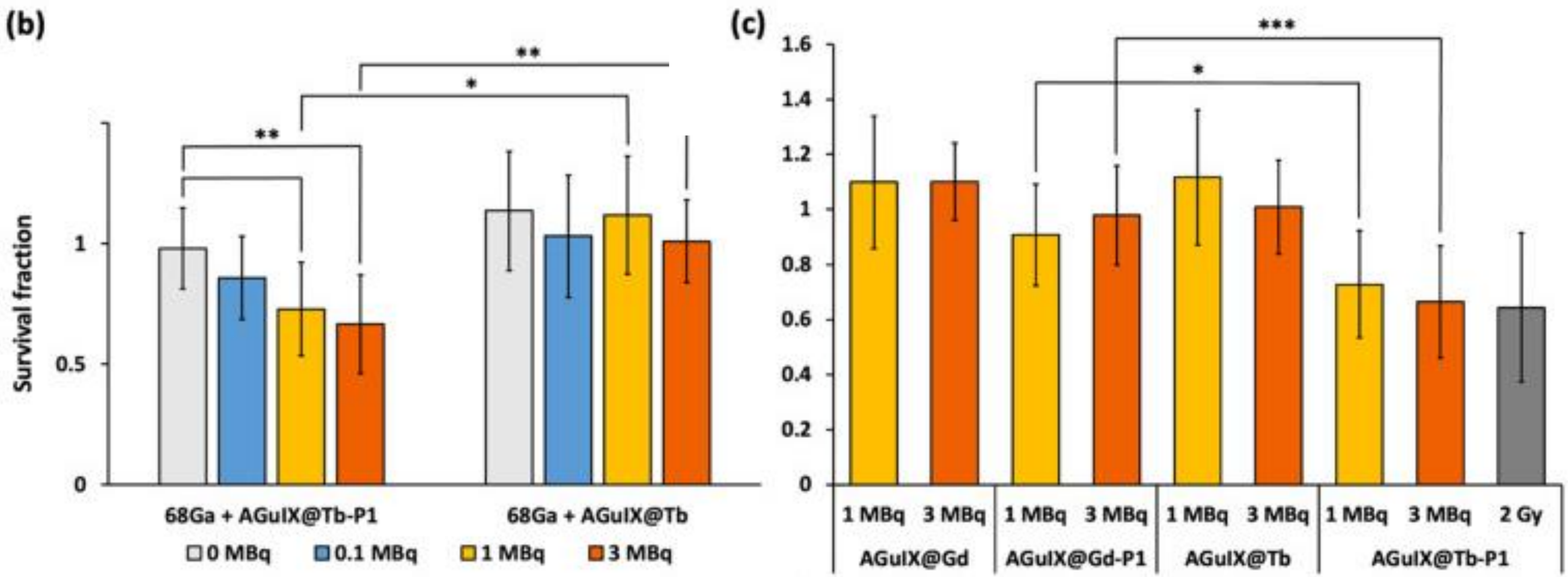
SINGLET OXYGEN PRODUCTION



Kinetics of singlet oxygen production by AGuIX@Tb-P1 under Gallium-68 exposure. 7.35 µM AGuIX@Tb-P1 (P1 equivalent), 10 µM fluorescent probe and 15–20 MBq([68]).

Schneller et al, Pharmaceuticals, 2023

Effect on cell survival

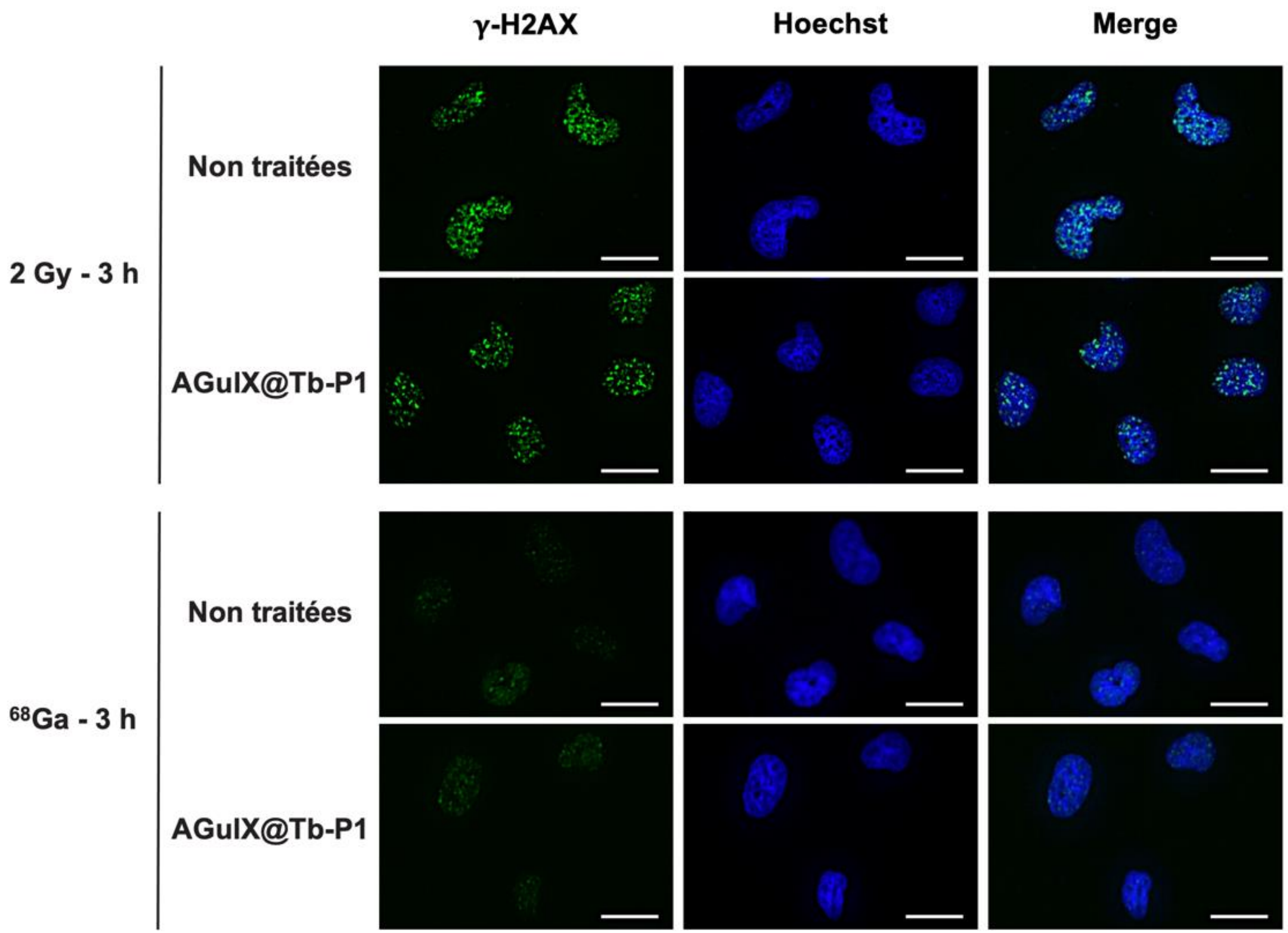


Impact of Gallium-68 deposition into U-251 MG cells.

- Scintillator improves treatment efficacy
- 3 MBq of ^{68}Ga reach the same effect than a 2 Gy X-ray-PDT irradiation
- 3 MBq of ^{68}Ga reach the same effect than a 4 Gy X-ray irradiation without PDT

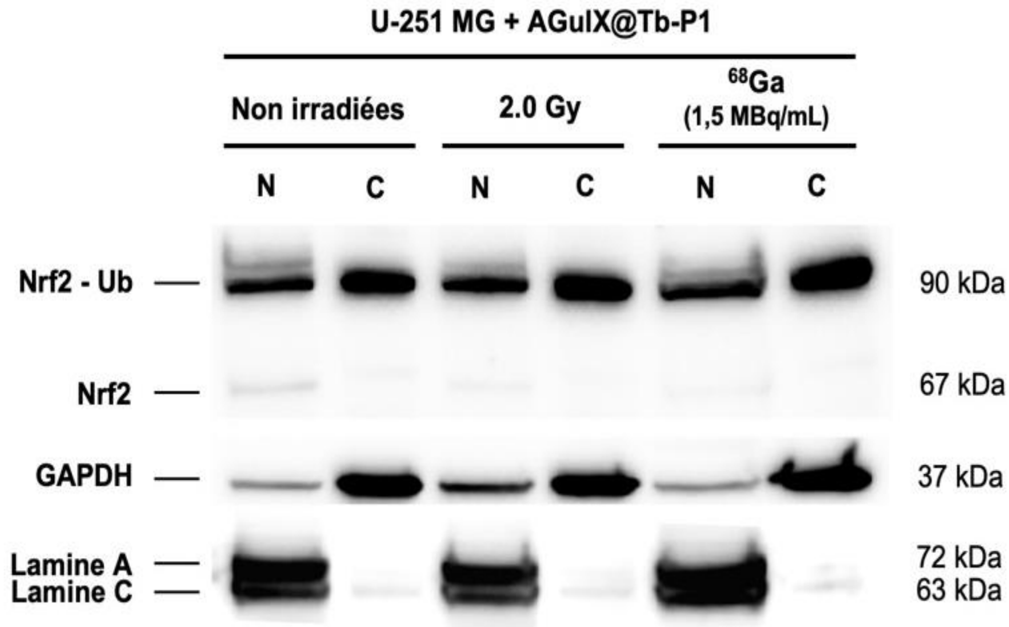
Schneller et al, Pharmaceuticals, 2023

EFFECT ON NUCLEAR DNA



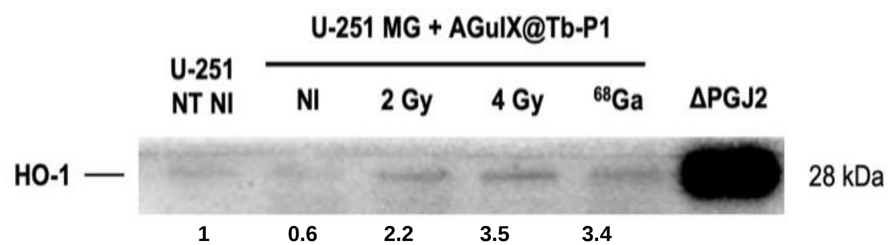
- 2 Gy X-ray + NP Tb-P1 ➔ increased H2AX fluorescence = cumulative effect on DNA
- 2 Gy X-ray + NP Tb ➔ H2AX fluorescence not increased = no radiosensitizing effect from Tb
- 3 MBq ^{68}Ga (~10^{-4} Gy) ➔ Basal H2AX signal = no DNA alteration

EFFECT ON OXIDATIVE STRESS RESPONSE



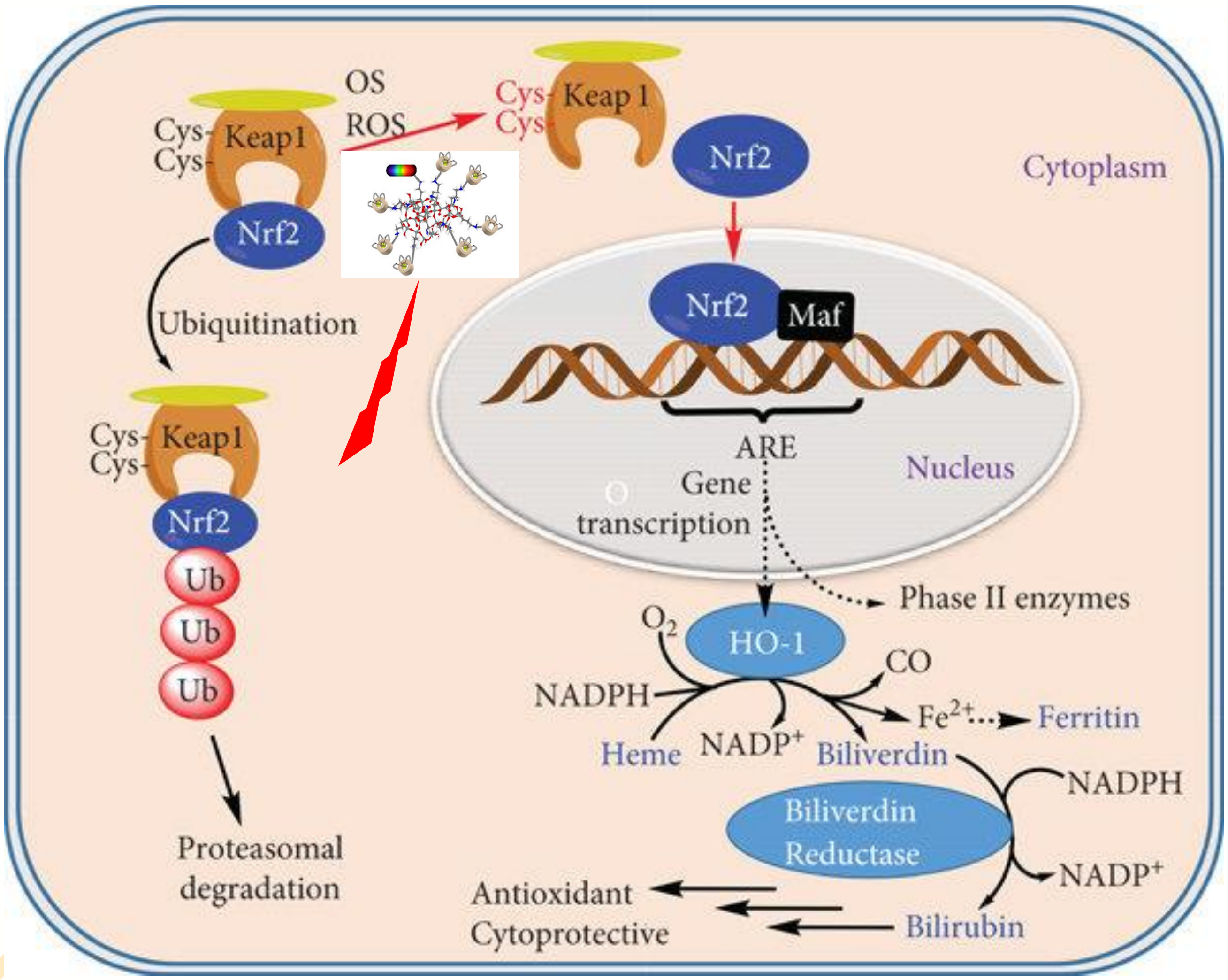
N: NUCLEAR SAMPLES, C: CYTOPLASMIC SAMPLES

- Nuclear Ubiquitinated Nrf2 increased after X-ray or ^{68}Ga irradiation ➔ transcriptional activity increased



- HO-1 increased with irradiation ➔ increased anti-oxidative activity
- 3 MBq ^{68}Ga yields same HO-1 expression than X-ray 4 Gy

EFFECT ON OXIDATIVE STRESS RESPONSE



Conclusion

- **High energy charged particles produce enough Cerenkov photons to induce a PDT effect**
- **Cerenkov-induced PDT can kill cancer cells with a much lower deposited dose compared to radiation therapy**
- **Cell death is not linked to nuclear DNA damage**
- **Oxidative stress seems to be the main involved pathway**