Gold Nanoparticles as a Potent Radiosensitizer: A Transdisciplinary Approach from Physics to Patient

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Radiotherapy

Major cancer treatment : 50% of patients are treated by radiotherapy

Goal: Deposition of a lethal dose of ionizing radiation in the tumour

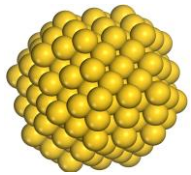
Irradiation

DNA damages

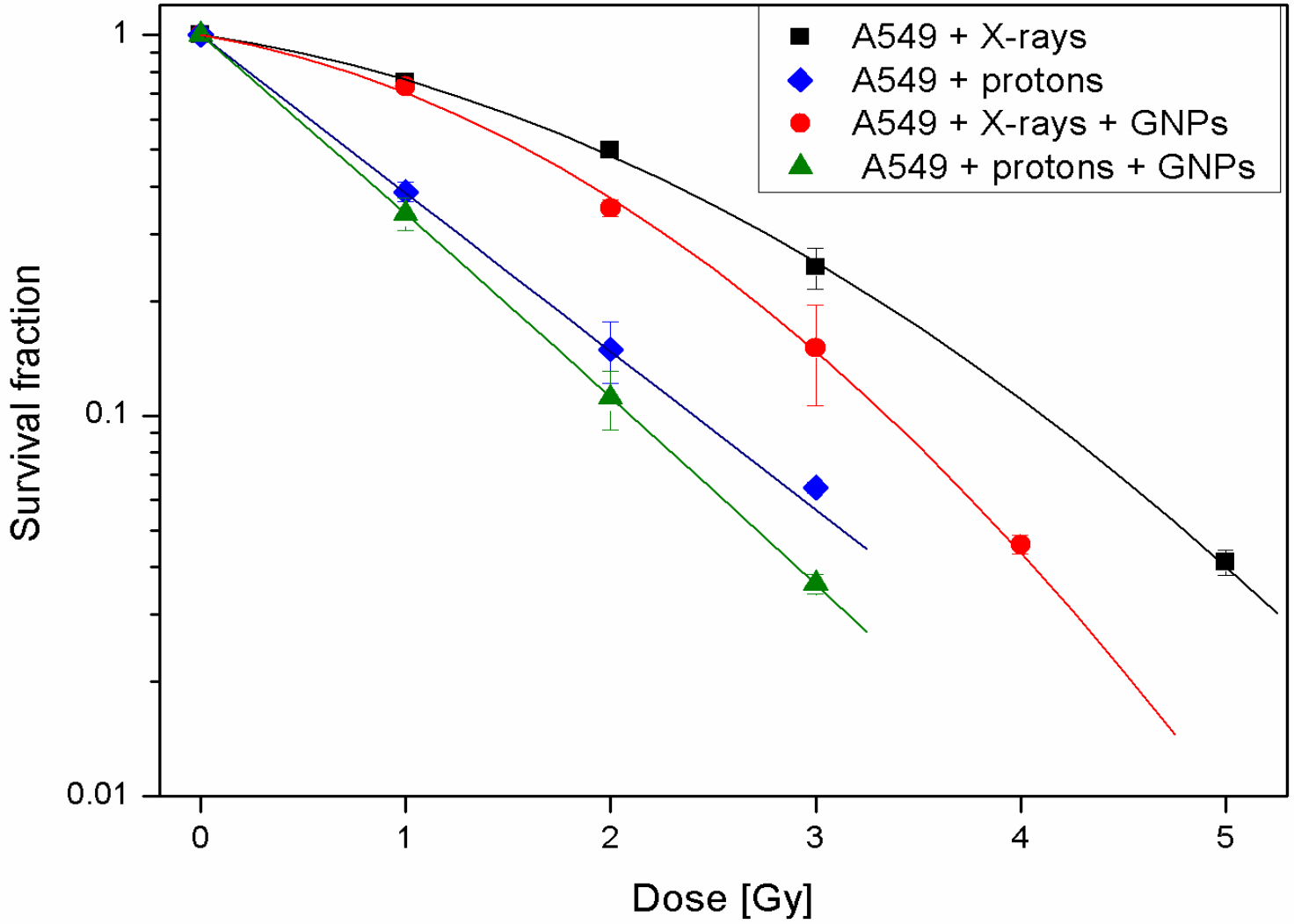
Cancer cell death

Main limitation: Dose received by the healthy tissue surrounding the tumor

Increase the dose deposition in tumour compared to healthy tissue



In vitro irradiation



Penninckx *et al.* , *Nanomedicine*, 2018

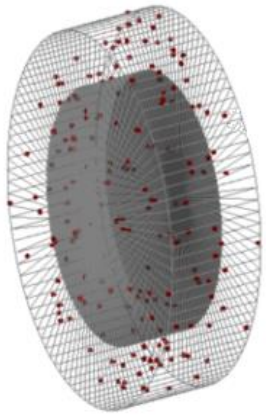
Questions

1. What are the mechanisms responsible for this radiosensitization effect ?

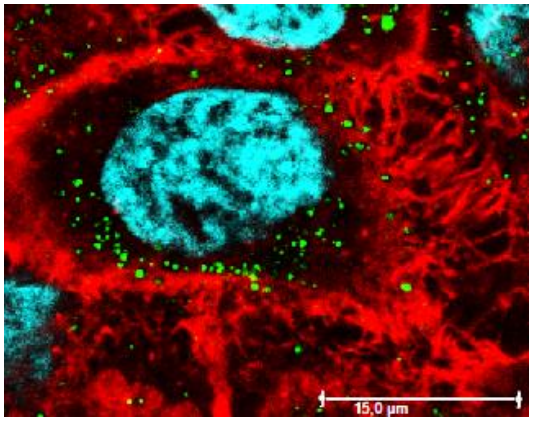
2. How do mechanistic findings influence the clinical translation ?

Physical contribution

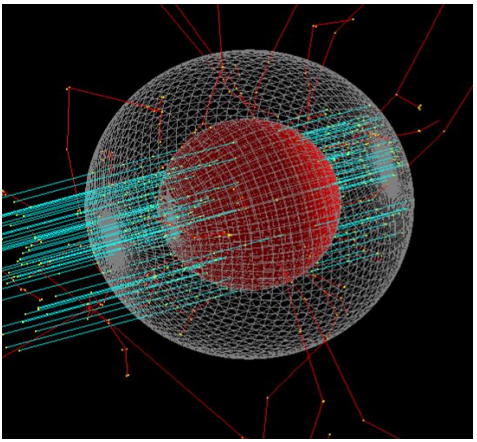
Target : 1 cell containing 2.10^5 GNPs

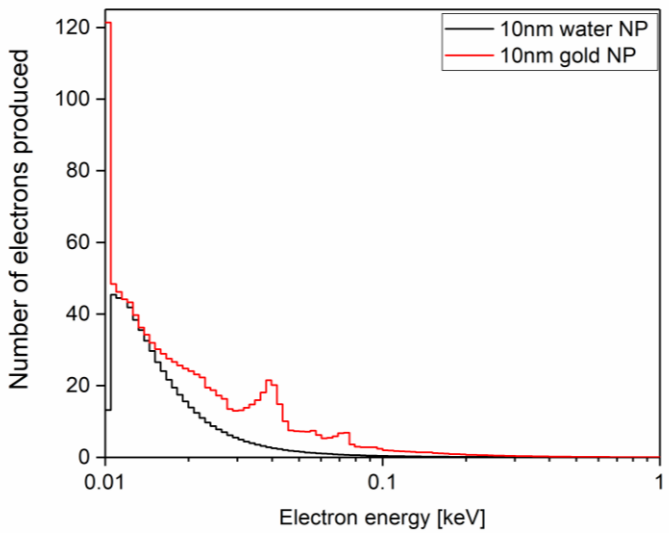


In a realistic cell geometry, only 1% of sent projectiles hit GNPs



Target : 1 GNP



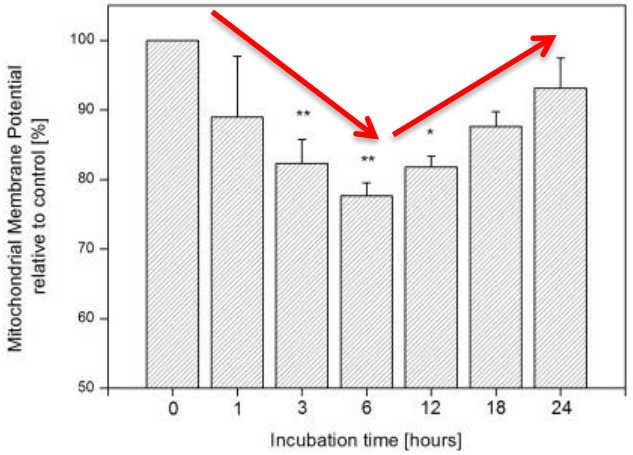


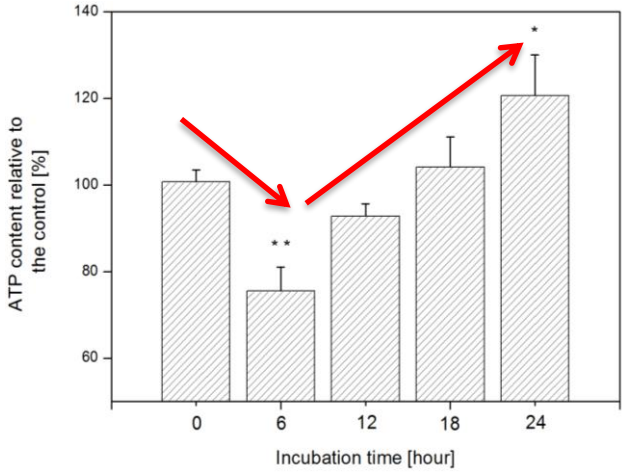
Dose enhancement is restricted 10 nm around GNP surface

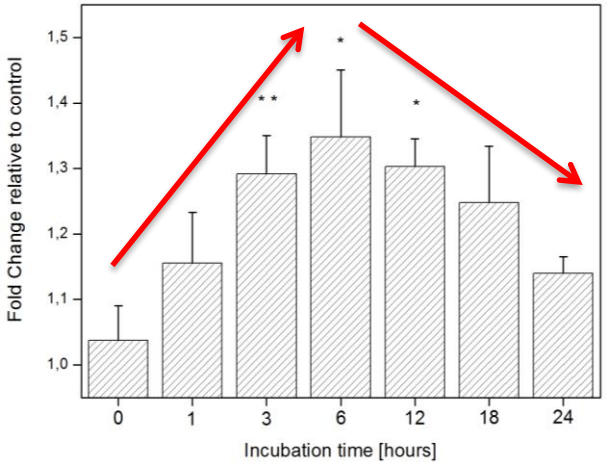
Heuskin et al., *Medical physics*, 2017 Hespeels *et al. , Phys. Med. Biol.*, 2019

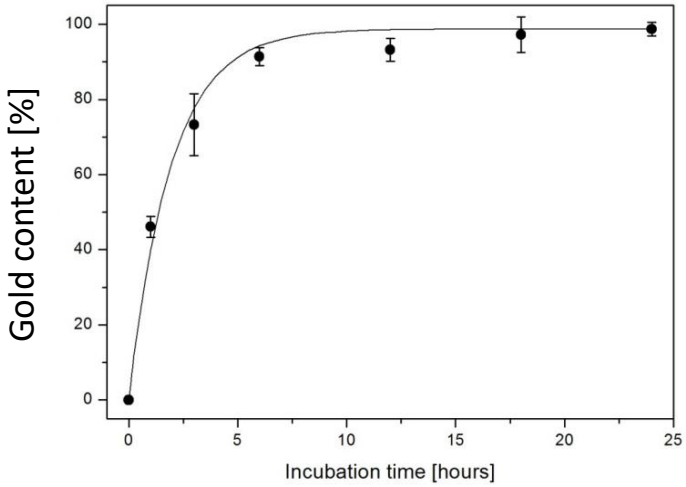
Biological contribution

Do GNPs induce change in biological pathways ?









Penninckx *et al.* , *Nanomedicine*, 2018

Biological contribution

Maximal gold content

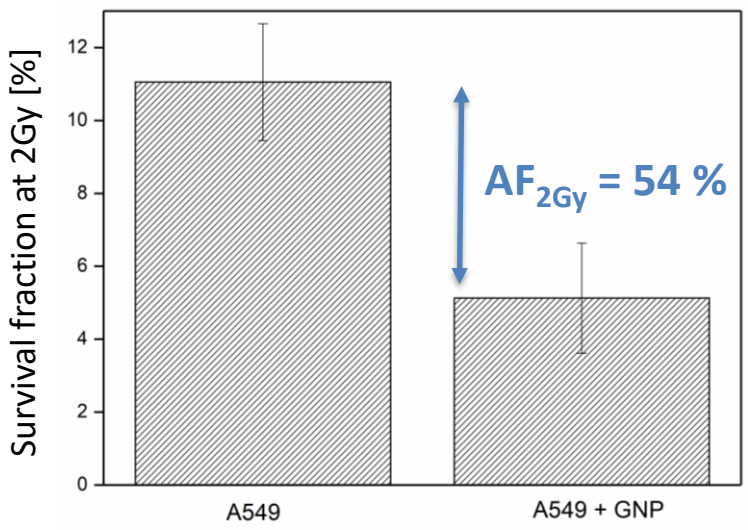
Maximal mitochondrial membrane depolarisation

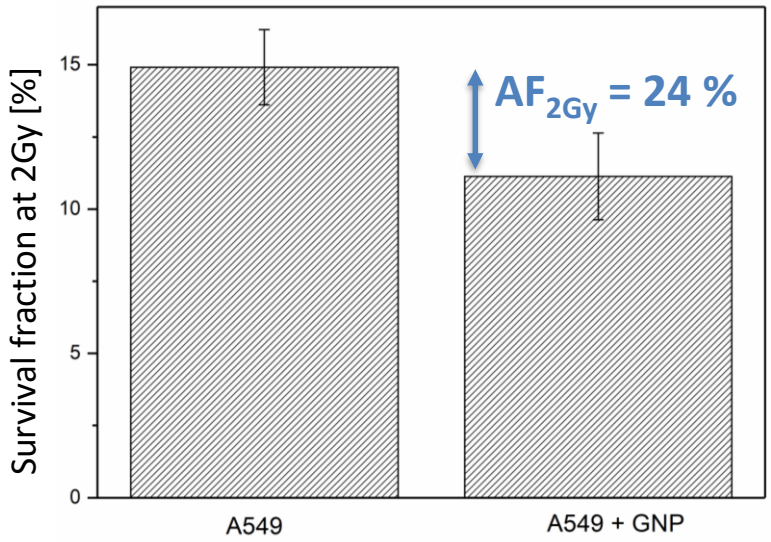
Maximal oxidative stress

Maximal gold content

Mitochondria repolarized at 90 %

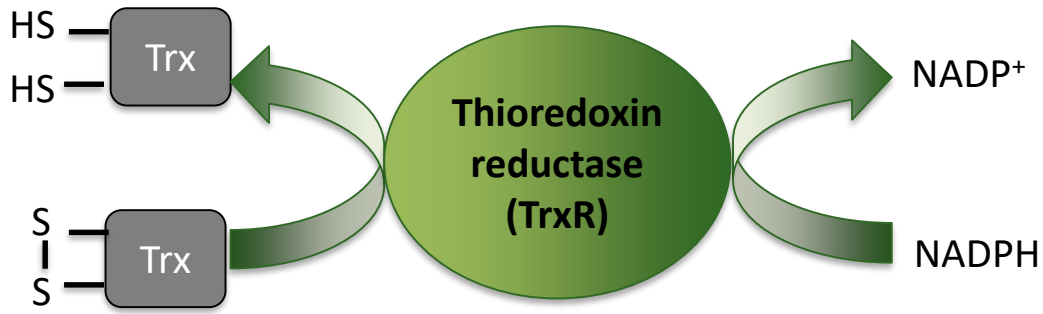
Small oxidative stress



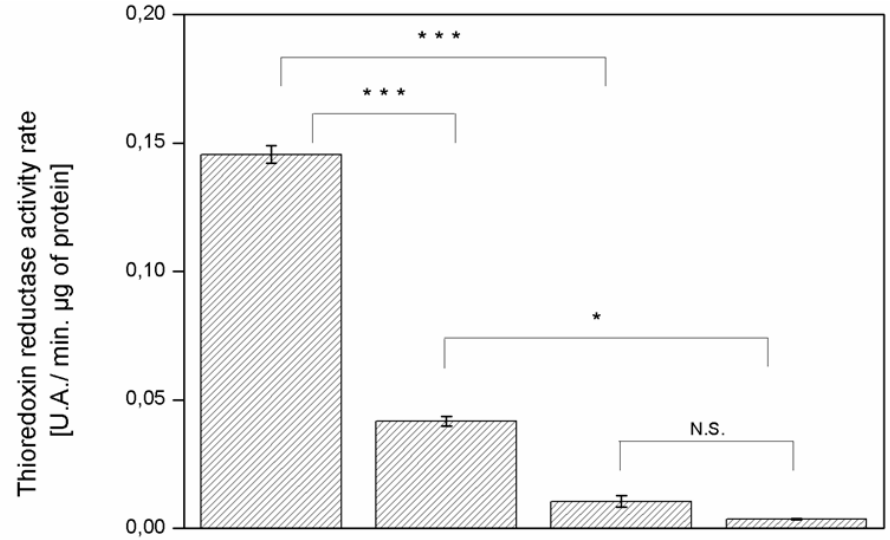


Penninckx *et al.* , *Nanomedicine*, 2018

Biological contribution

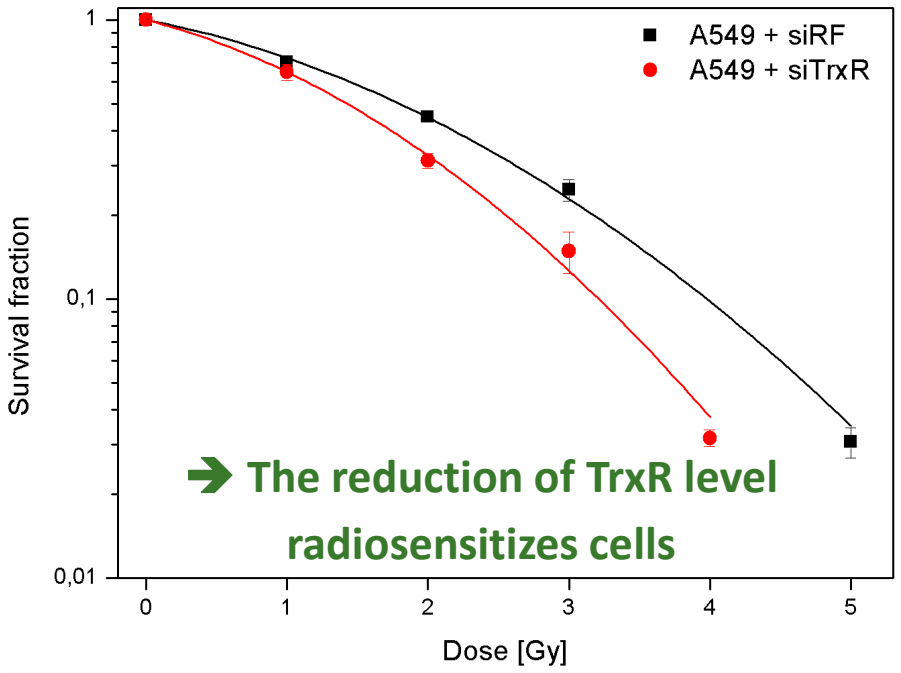


Antioxidant enzyme



GNPs	-	+	-	+
Inhibitor	-	-	+	+

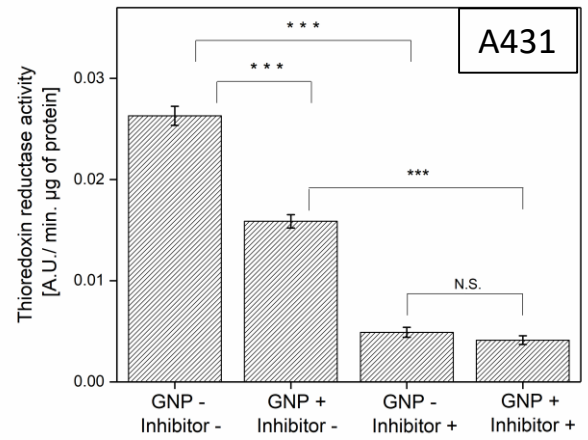
➔ **GNPs inhibit TrxR**

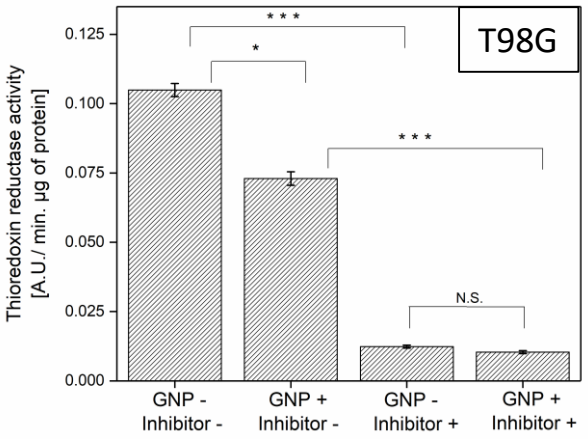


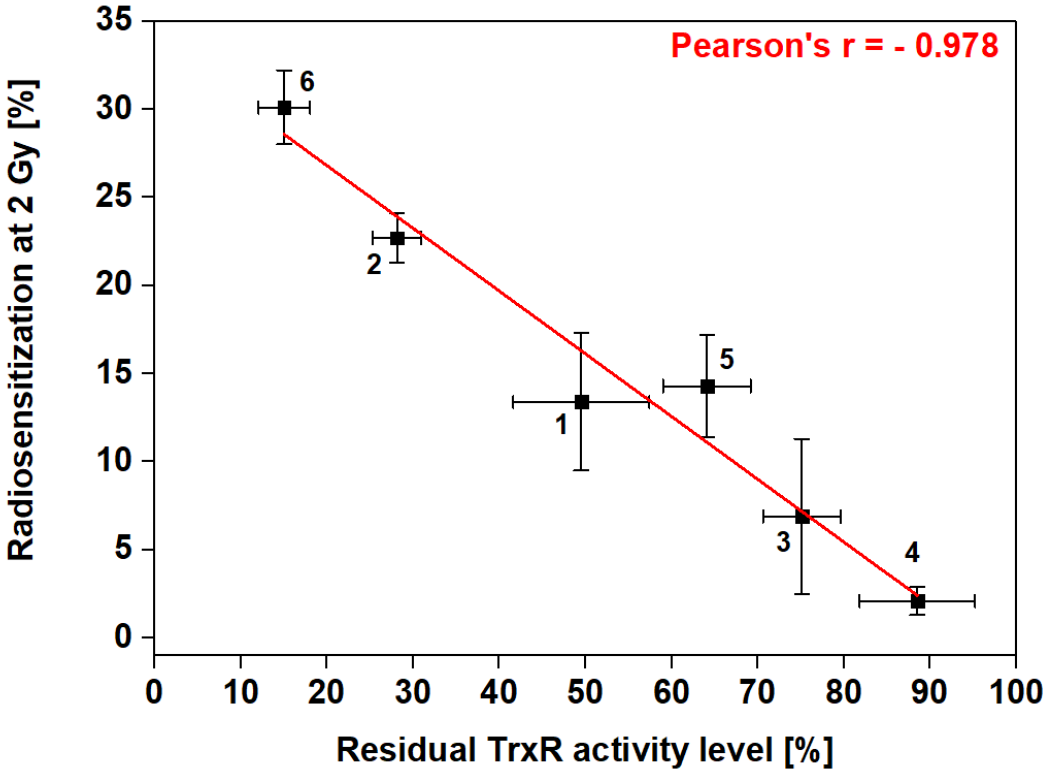
➔ **The reduction of TrxR level radiosensitizes cells**

Penninckx *et al.* , *Nanomedicine*, 2018

Biological contribution



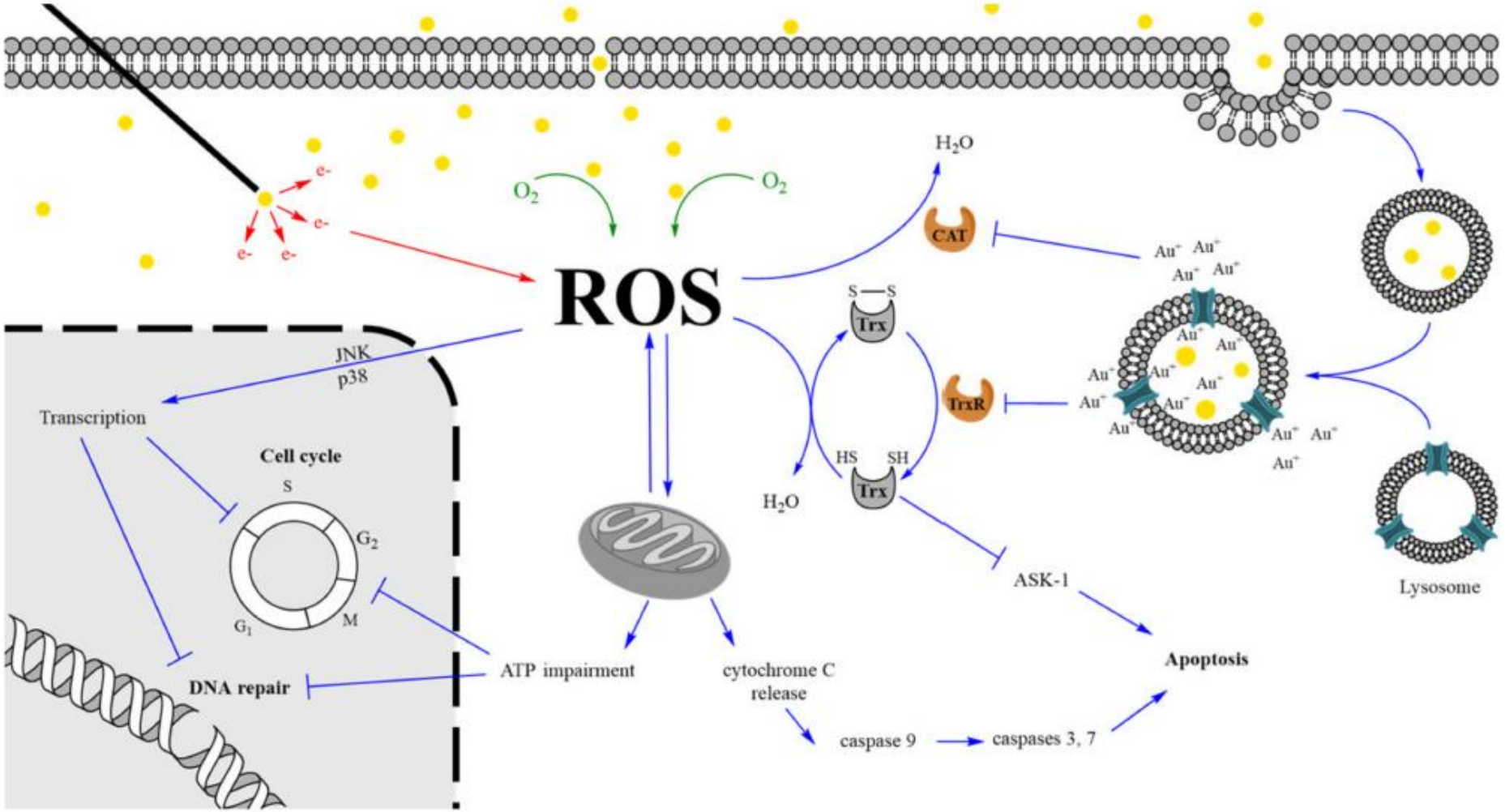




1. A431 cells
2. A549 cells
3. MDA-MB-231 cells
4. PANC1 cells
5. T98G cells
6. TrxR-invalidated A549 cells

(One-way ANOVA tukey test, *p< 0.05 ; *** p < 0.001; N.S. = No significant).

Multifactorial contributions



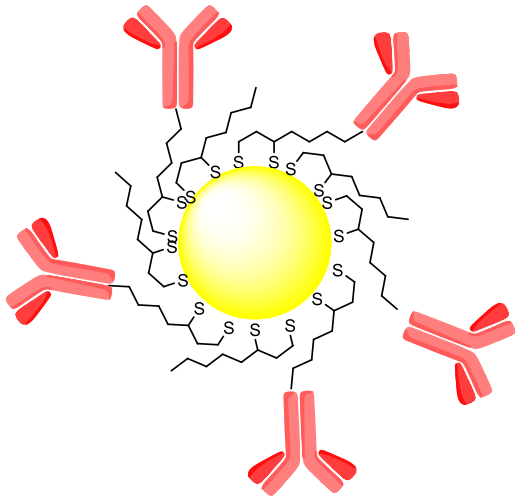
Penninckx *et al.* , *Cancers*, 2020

Objective

1. What are the mechanisms responsible for this radiosensitization effect ?

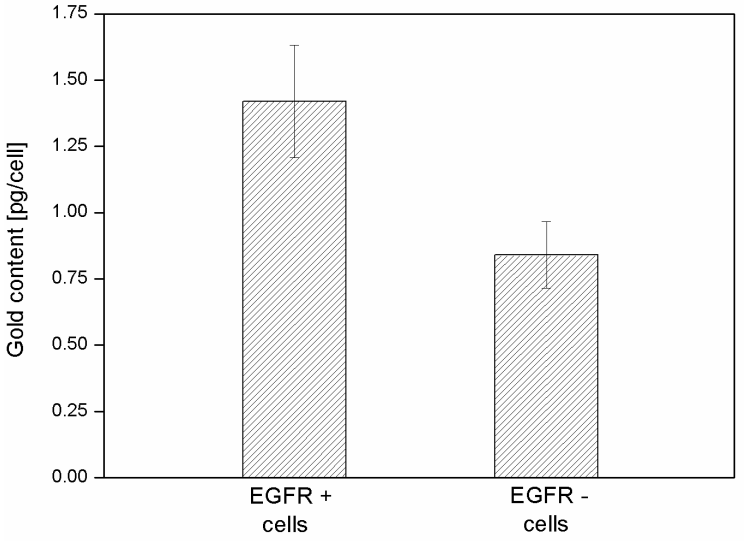
2. How do mechanistic findings influence the clinical translation ?

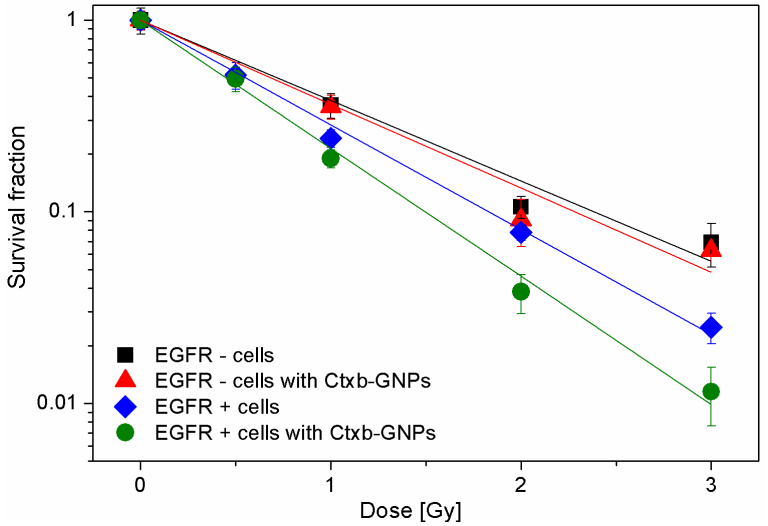
Tumor targeting



GNPs coupled to EGFR antibody

Patent, UNamur





Li, Penninckx *et al.* , *Nanomedicine*, 2019

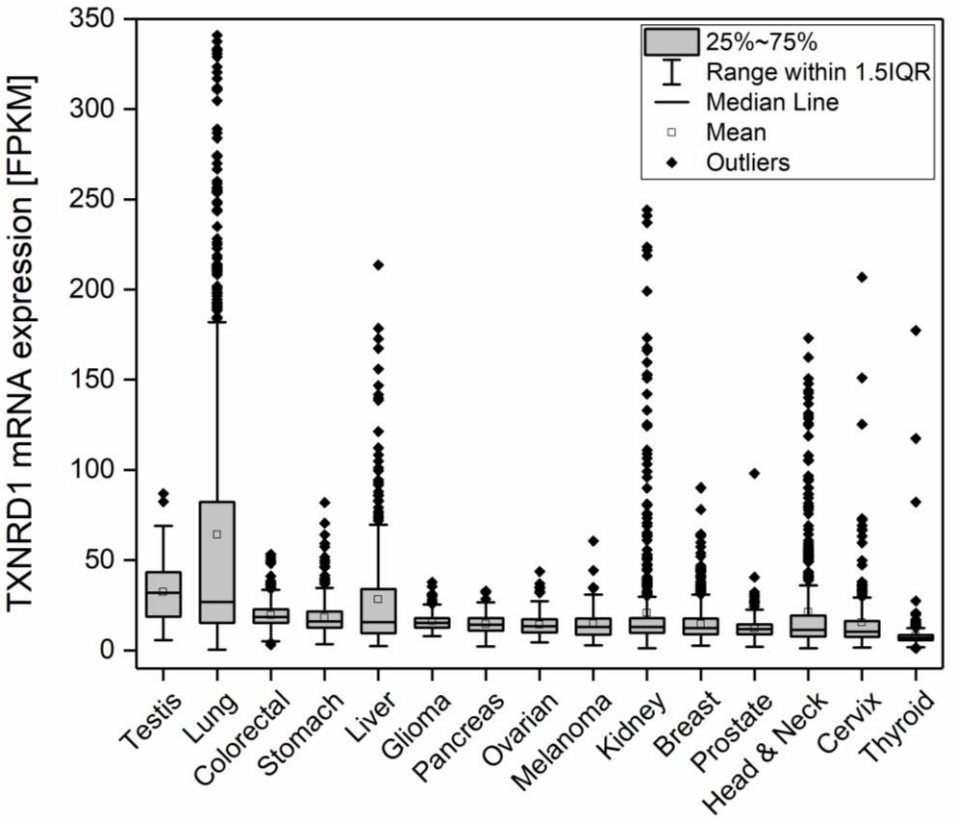
Clinical indication

Physics

Maximise the dose enhancer effect by using low-energy photons (< 50 keV)

- ✓Intraoperative RT
- ✓Brachytherapy

Biology

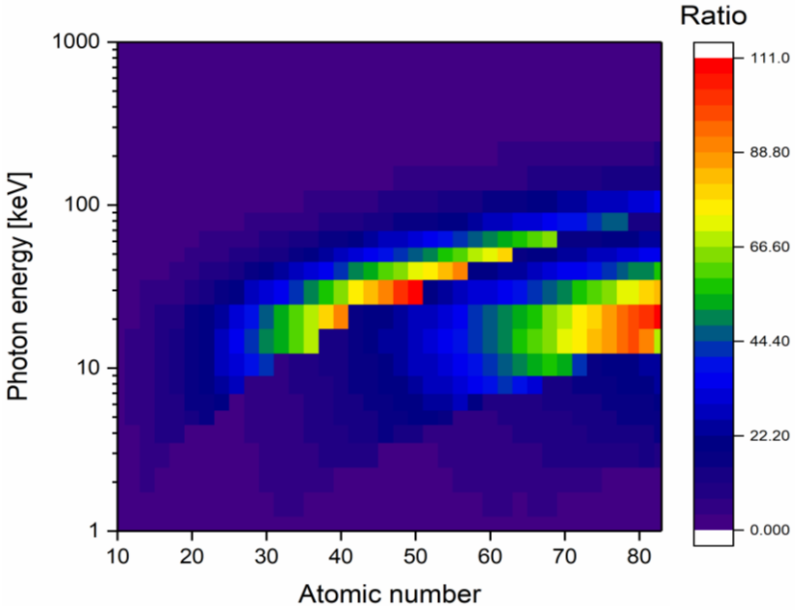


Median survival time in lung cancer patients:

Low TrxR expression : 102 months
High TrxR expression : 44 months

Gold as nanoparticles ?

Physics



- ✓ Bismuth (z = 83)
- ✓ Gold (z = 79)
- ✓ Platinum (z = 78)
- ✓ Hafnium (z = 72)

- ✓ Gadolinium (z = 64)
- ✓ Silver (z = 47)

Biology

1. **Good ions candidates for TrxR inhibition**

2. **Fast ion release in acidic conditions**

   - ✓ Silver
   - ✓ Iron
   - ✓ Gadolinium

Take home message

- ✓ Gold nanoparticles enhance cell mortality after exposure to ionizing radiation, playing the role of dose enhancer & radiosensitizer
- ✓ The mechanism responsible for this effect seems to be a complex combination of physical, chemical and biological contributions where the role of ROS is central
- ✓ More preclinical researches on nano-object optimization are needed to go towards clinical translation

Acknowledgment

S. Lucas
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N. Reynaert

Open to collaboration

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