

# Impact of gold nanoparticles on macrophage redox signaling

A. Boudier



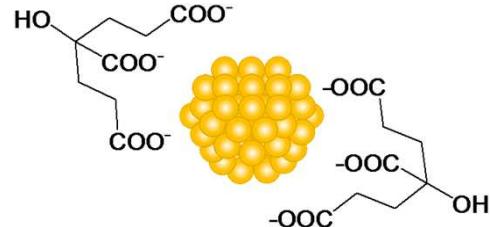
# Clinical trials

Name	Gold nanoparticle structure (size)	Drug	Clinical trials	Indication
Aurimune™ CYT-6091	TNF and PEG-Thiol to the surface of colloidal gold nanoparticles (27 nm)	Tumor necrosis factor alpha	Under phase 2 evaluation	solid tumors
AuroLase®	gold metal shell and a silica core (150 nm)	Photothermal therapy	Under Phase 1 evaluation	head and neck, prostate and lung tumors
Midaform™ Insulin PharmFilm	Insulin, stabilized on nanoparticles (< 2 nm)	Insulin	Phase 1 completed	diabetes



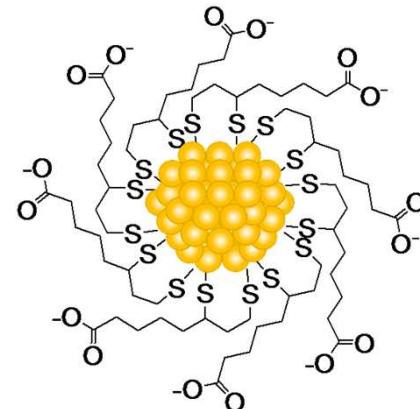
# Gold nanoparticles

Stabilized with citrate ions  
Au-Citrate



Classical ones

Linked with dihydrolipoic acid  
Au@DHLA

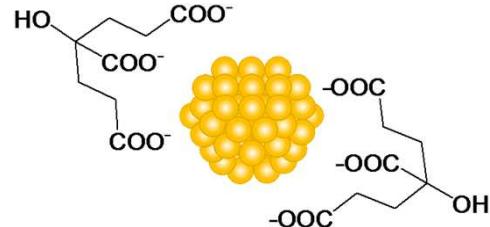


Platforms for drug grafting

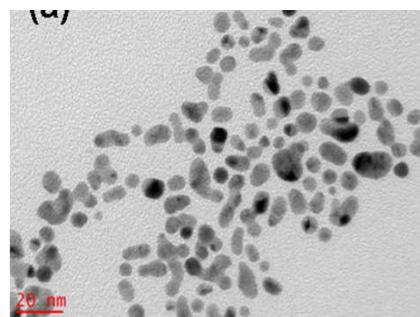


# Gold nanoparticles

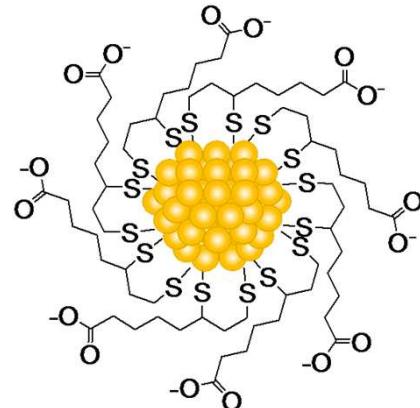
Stabilized with citrate ions  
**Au-Citrate**



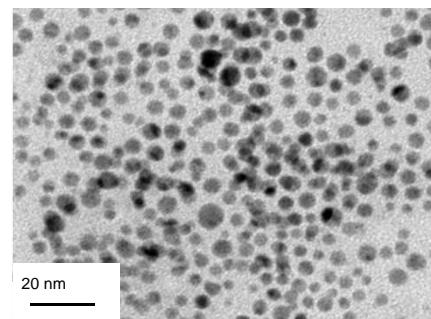
D<sub>h</sub> = 6.5 ± 1.7 nm



Linked with dihydrolipoic acid  
**Au@DHLA**



D<sub>h</sub> = 7.2 ± 1.2 nm  
[S]/[Au] = 0.41 ± 0.02



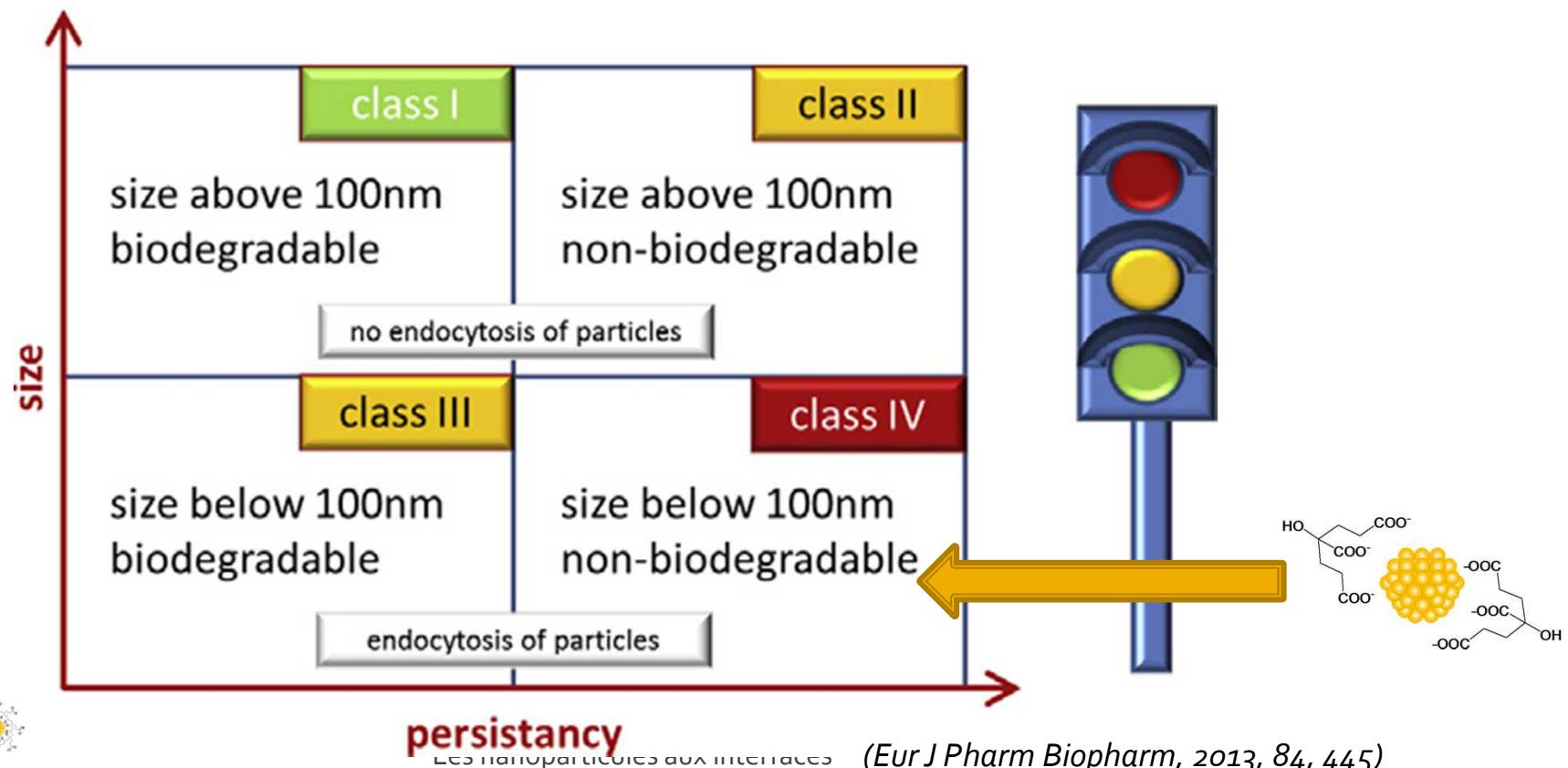
ACS Appl Mater Interfaces,  
2012, 4, 5790

# Biocompatibility ?

General dogma: « Gold is inert »

True for Au(0) but what about gold under a nanoparticulate form

## Nanotoxicological classification system (NCS)



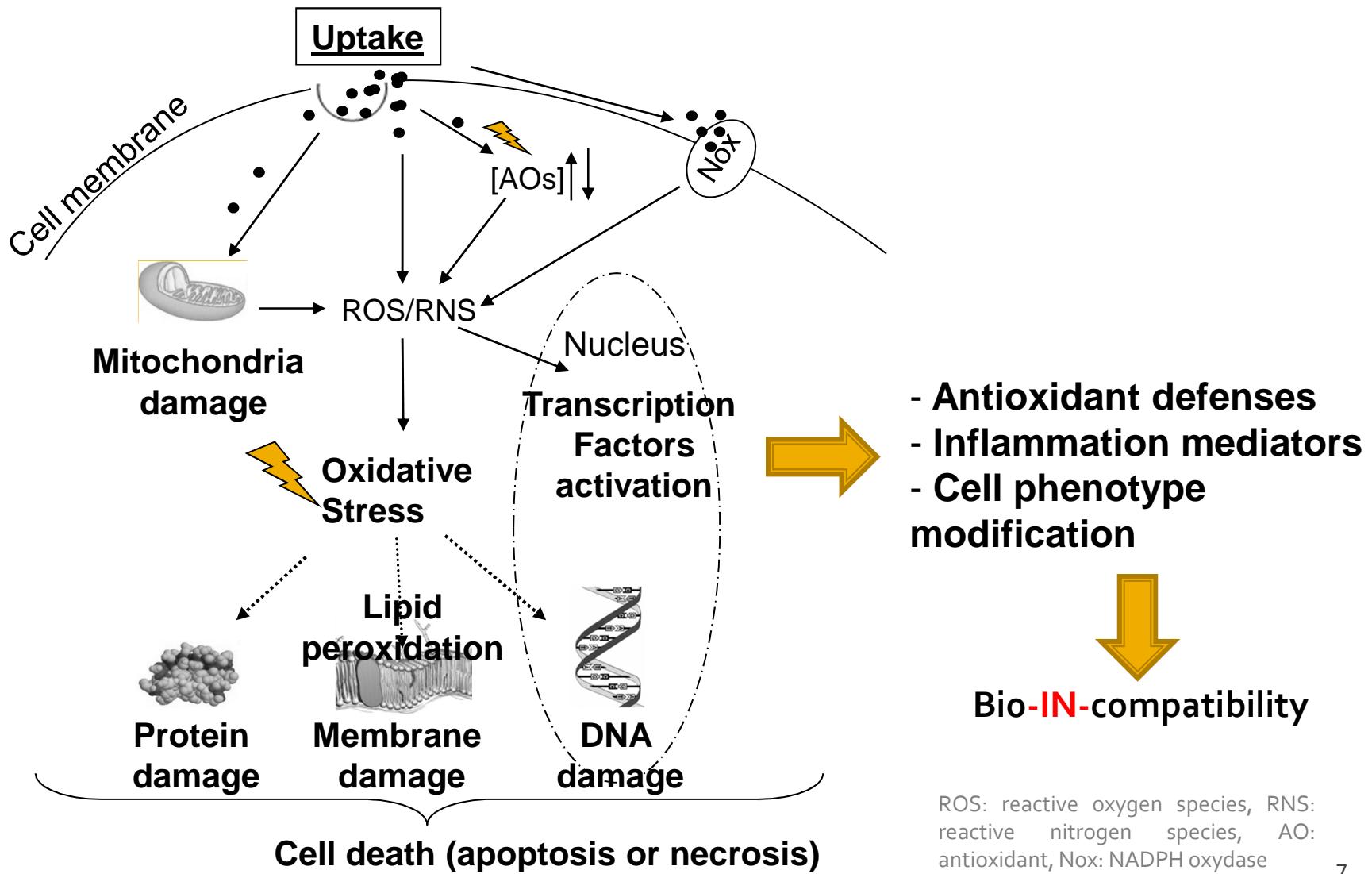
# Biocompatibility ?

- Element that do not induce any cell phenotype modification
  - Good cytotoxicity
  - No modification of the immunological status (inflammatory responses)
  - Preservation of antioxidant defenses
    - Redox signaling: preservation of oxidant/antioxidant balance
    - Oxidative stress: disturbance of redox signaling towards pro-oxidant elements



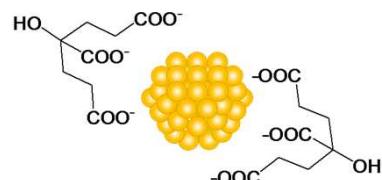
# Redox homeostasis implication in biocompatibility

Talanta 2013, 116, 753

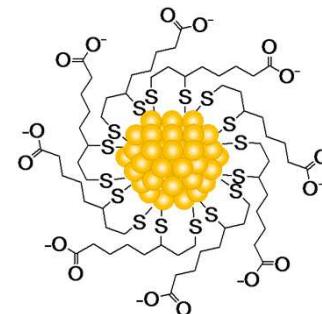


# Cell model

*Int J Pharm*, 2012, 438, 107



Au-citrate

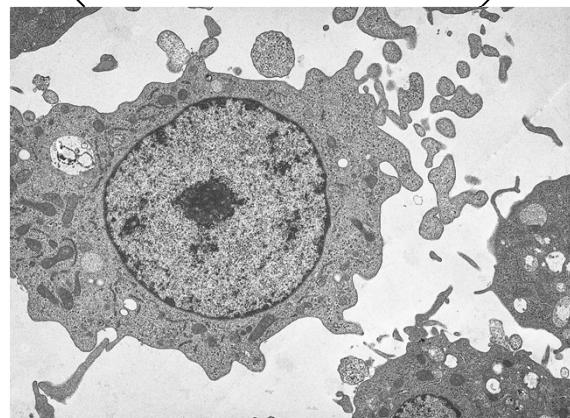


Au@DHLA

[AuNP] = 10 nM

Viability ca. 80 %

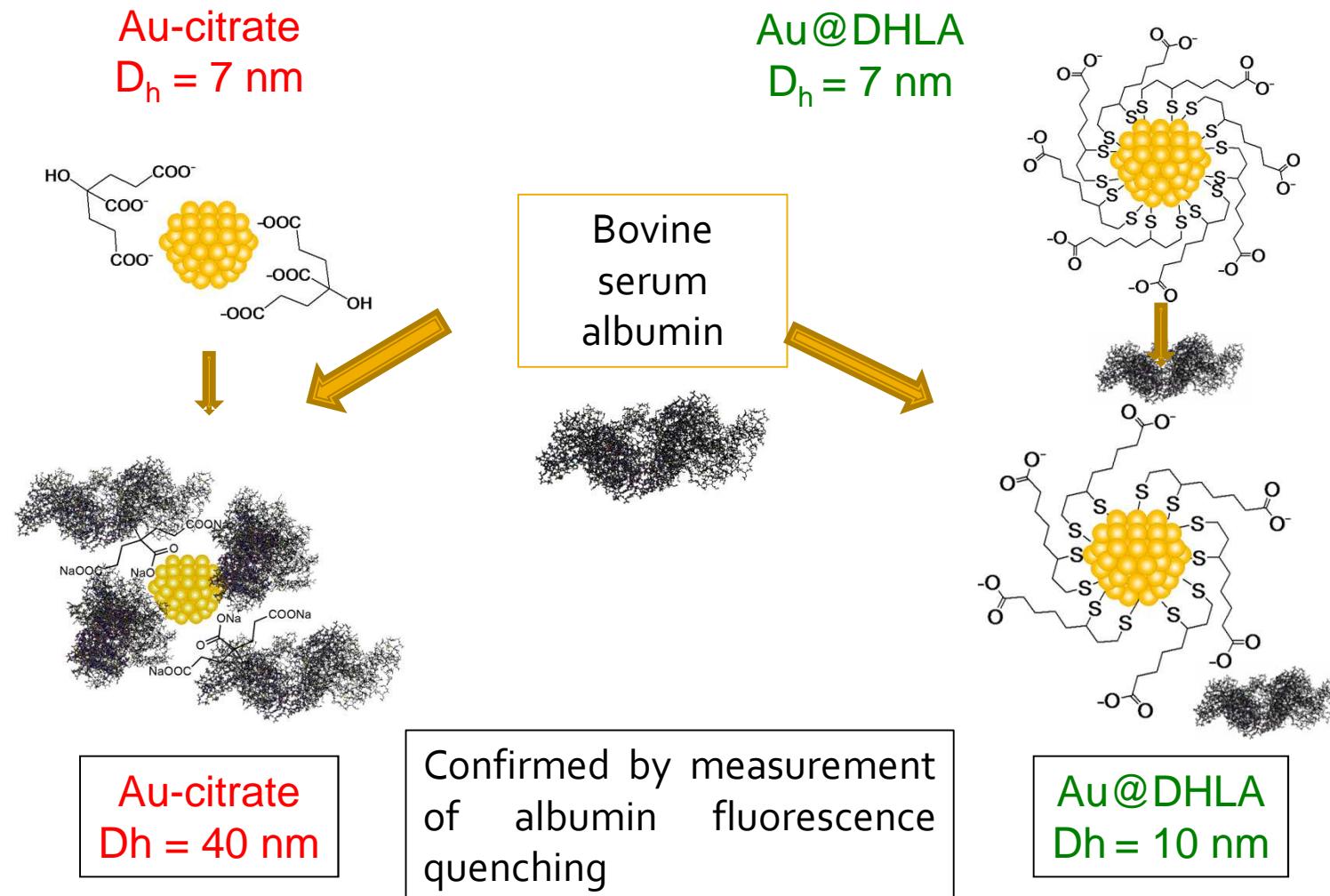
**Model cell line :**  
NR8383 rat  
macrophages



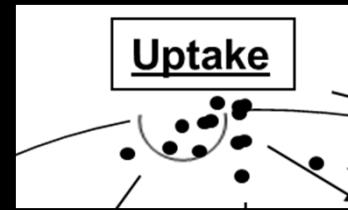
"Les nanoparticules aux interfaces"



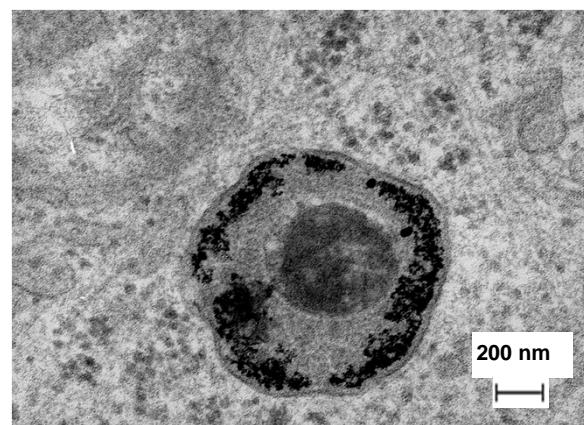
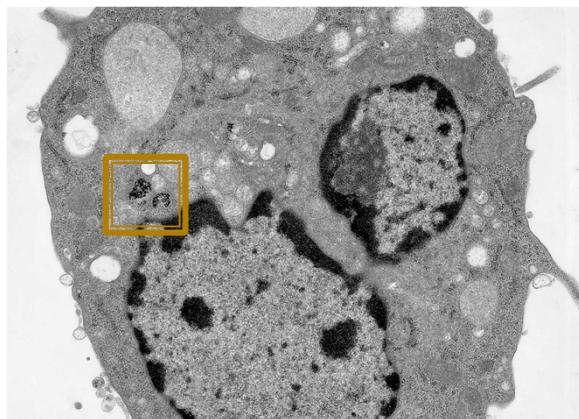
# Interaction with culture medium



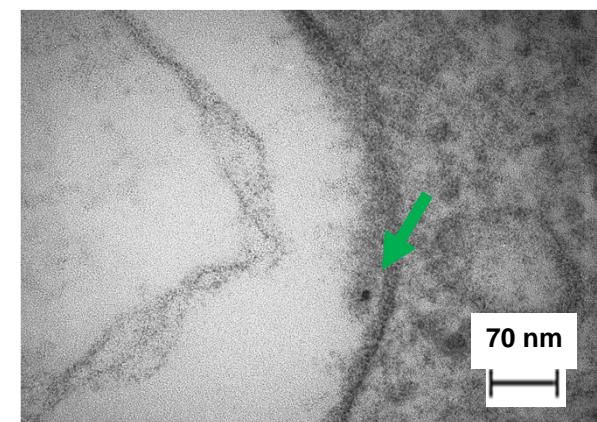
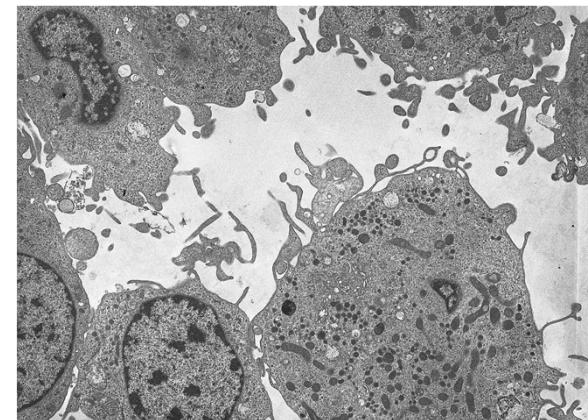
# Uptake



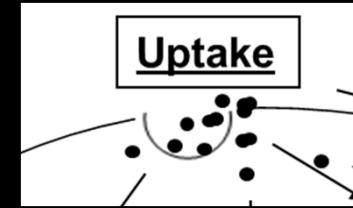
Au-citrate



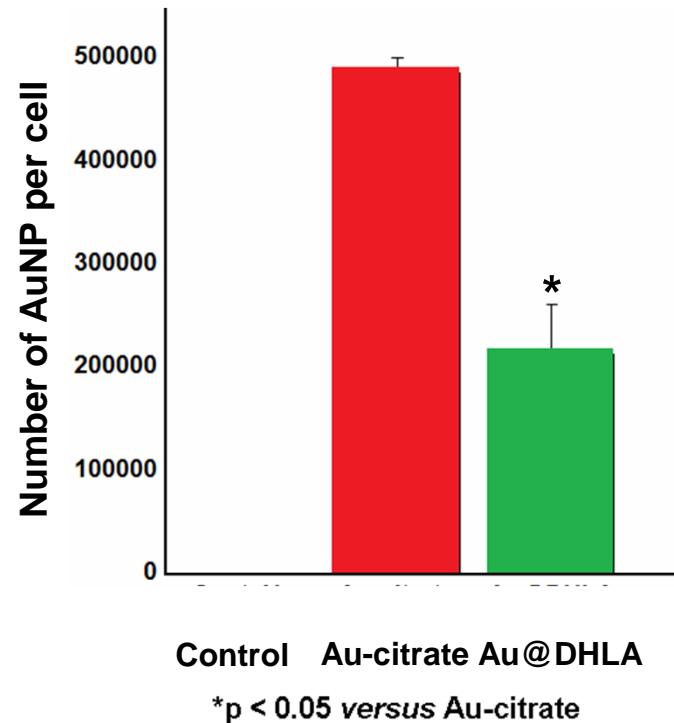
Au@DHLA



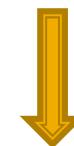
# Uptake



## Induced Coupled Plasma-Mass Spectrometry



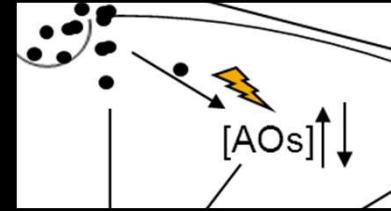
- Au@DHLA= Two times less internalized



Au@DHLA seem « stealther » than AuNP-citrate

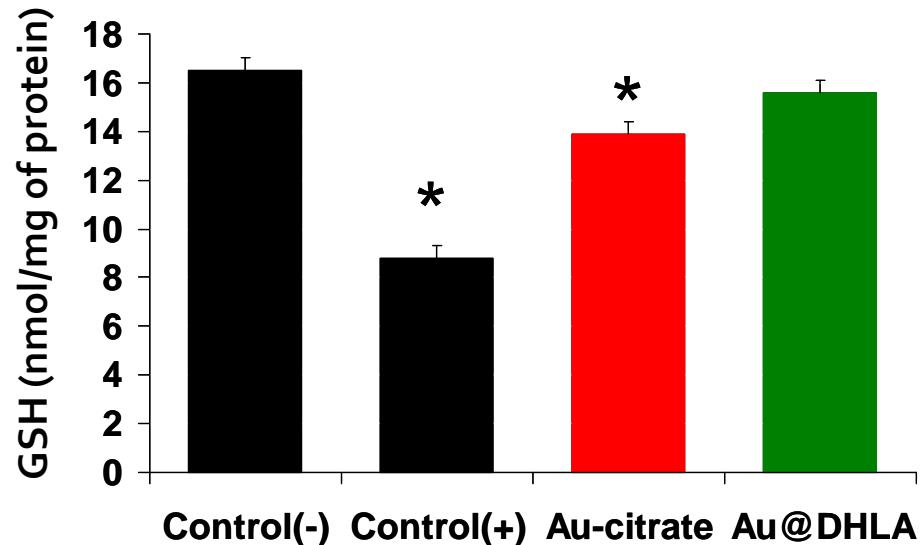


# Antioxidant content



## Intracellular reduced glutathione (GSH)

using naphthalene- 2,3-dicarboxyaldehyde (NDA) and fluorescence detection



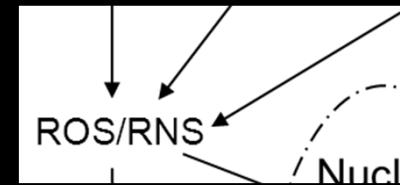
**Au@DHLA do not deplete intracellular GSH**

\* $p < 0.05$  versus control (-)

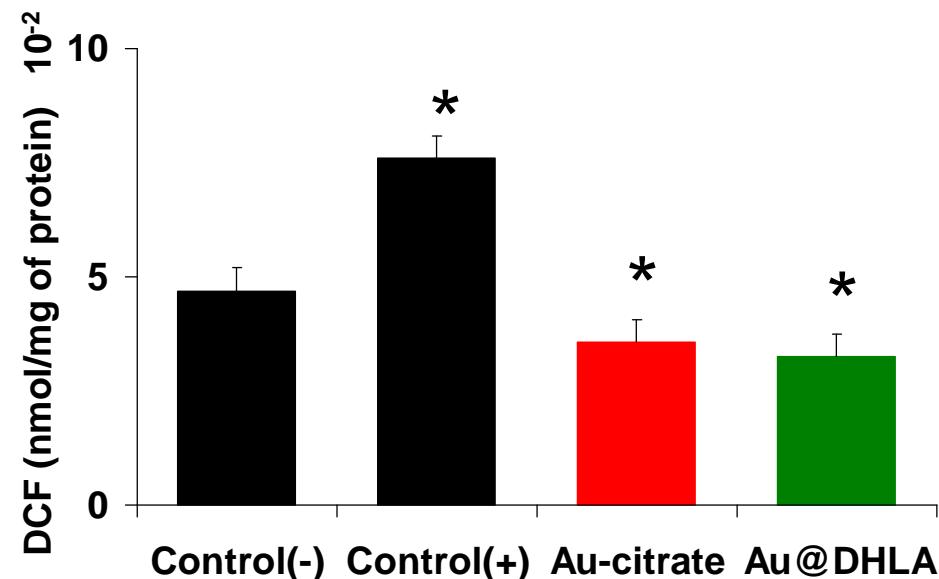
Control(-) cells without treatment  
Control(+) Polymeric NP (Eudragit® RS)



# Reactive oxygen species



Intracellular reactive oxygen species content(ROS)  
using 2,7-dichlorofluorescin diacetate (DCFH<sub>2</sub>-DA) and fluorescence detection



**Au@DHLA deplete  
intracellular ROS**

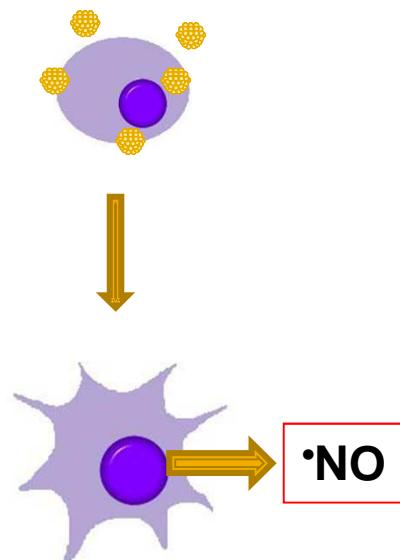
\* $p < 0.05$  versus control (-)

Control(-) cells without treatment  
Control(+) Polymeric NP (Eudragit® RS)

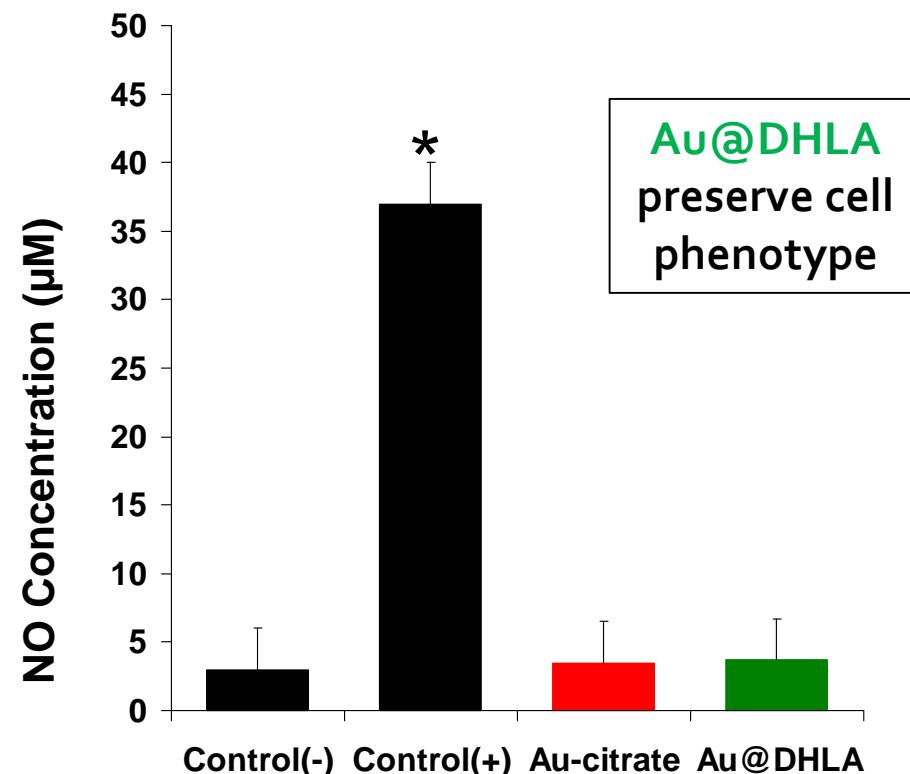
# Inflammatory status

- Antioxidant defenses
- Inflammation mediators
- Cell phenotype modification

Macrophages  
+ AuNP



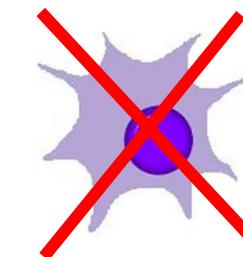
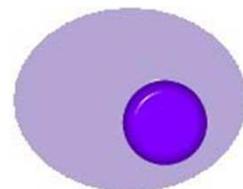
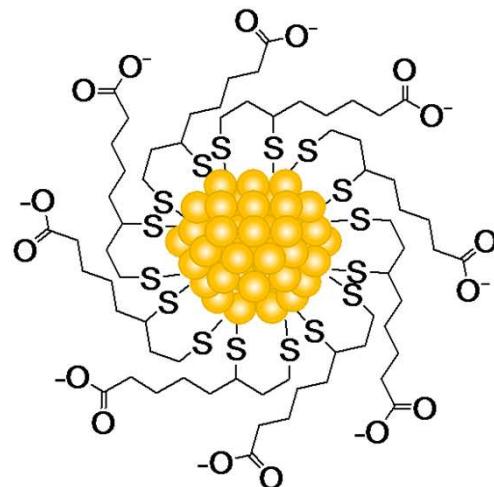
Activation ?



$\cdot\text{NO}$ : nitric oxide; control +: *lipopolysaccharides*; control -: cells without treatment      \* $p < 0.05$  versus control (-)



# Conclusion



- **Preservation of antioxidant defenses**
- **Preservation of cell phenotype**
- **No toxicity**



**Platform for drug delivery  
For antioxidant grafting**





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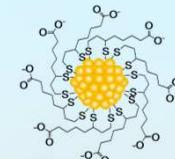


Cibles Thérapeutiques, Formulation et  
Expertise Préclinique du Médicament

Drug targets, formulation and  
preclinical drug assessment



Pr P. Leroy  
Dr A. Sapin-Minet  
Dr J. Tournebize  
J. Marinovic



Pr R. Schneider

"Les nanoparticules aux interfaces"

