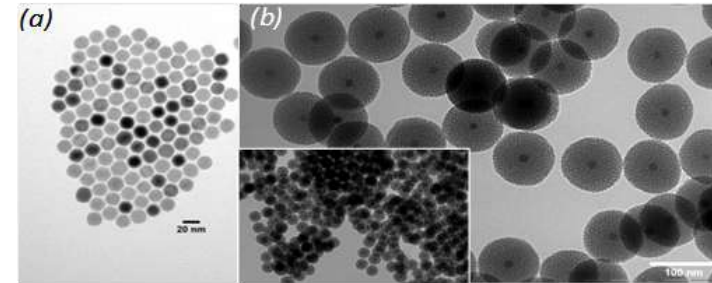


Clarence CHARNAY, Raymond EBABE, Jean-Paul CRISTOL  
and Eric BADIA

# Polyphénols greffés sur nanoparticules de silice mésoporeuse : vers une diminution de leur cytotoxicité

## Grande variété de nanoparticules inorganiques élaborées et étudiées en nanomédecine

- Métalliques: Or, Ag ...
- Metalloïdes : Si, Ge
- Oxydes :  $\text{SiO}_2$ ,  $\text{Fe}_3\text{O}_4$ ,  $\text{HfO}_2$ , système core-shell
- Quantum dots : CdSe/ZnS , CdTe/CdS, InP....
- Nanocarbone : nanotubes, graphenes...
- Système hybride : organosilice, MOF + polymères de coordination
- Systèmes multifonctionnels/composites : biocompatibilité, ciblage...



**Applications** : biodétection et diagnostique, thérapeutique, délivrance ciblée...

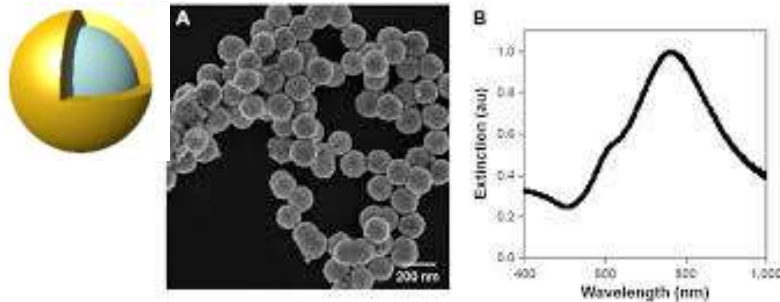
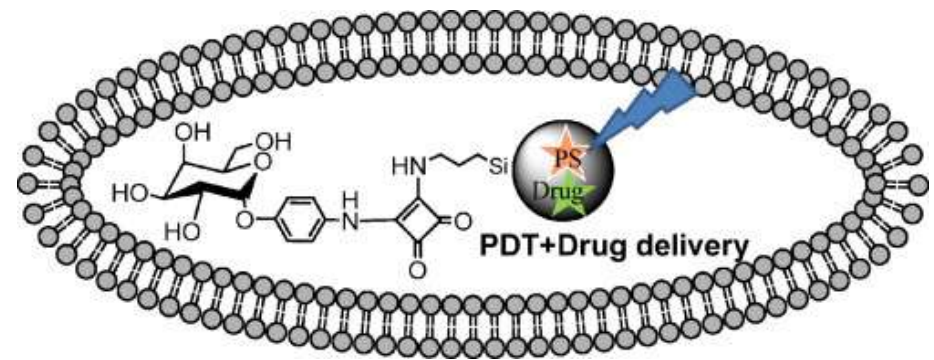


Figure 1. Characterization of the nanoshells used in this work.  
Notes: (A) Scanning electron micrograph of the nanoshells. (B) Extinction spectrum of the nanoshells.



### Thérapie photothermale

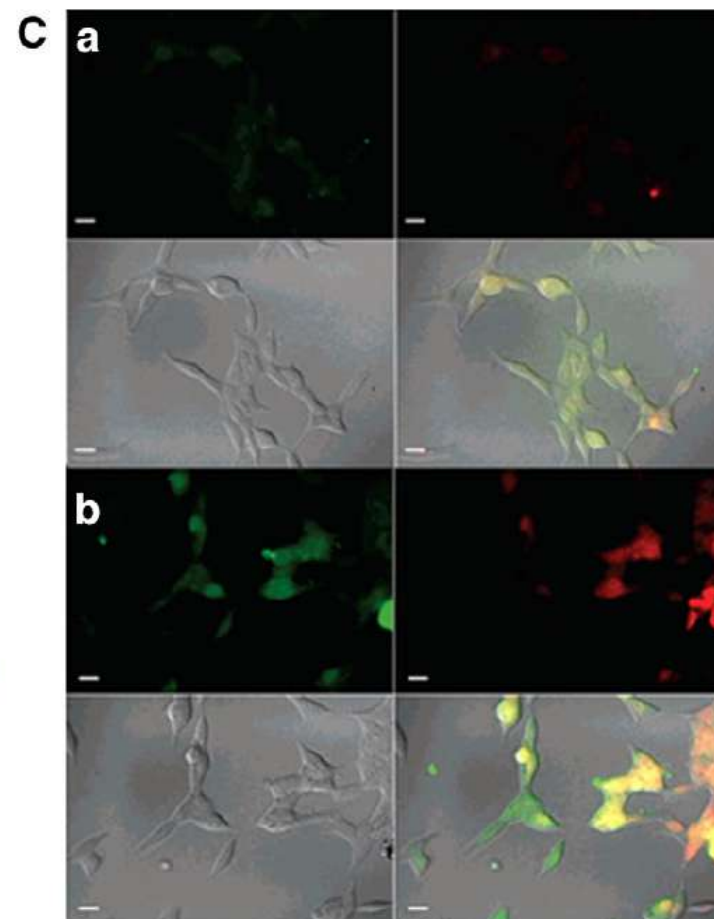
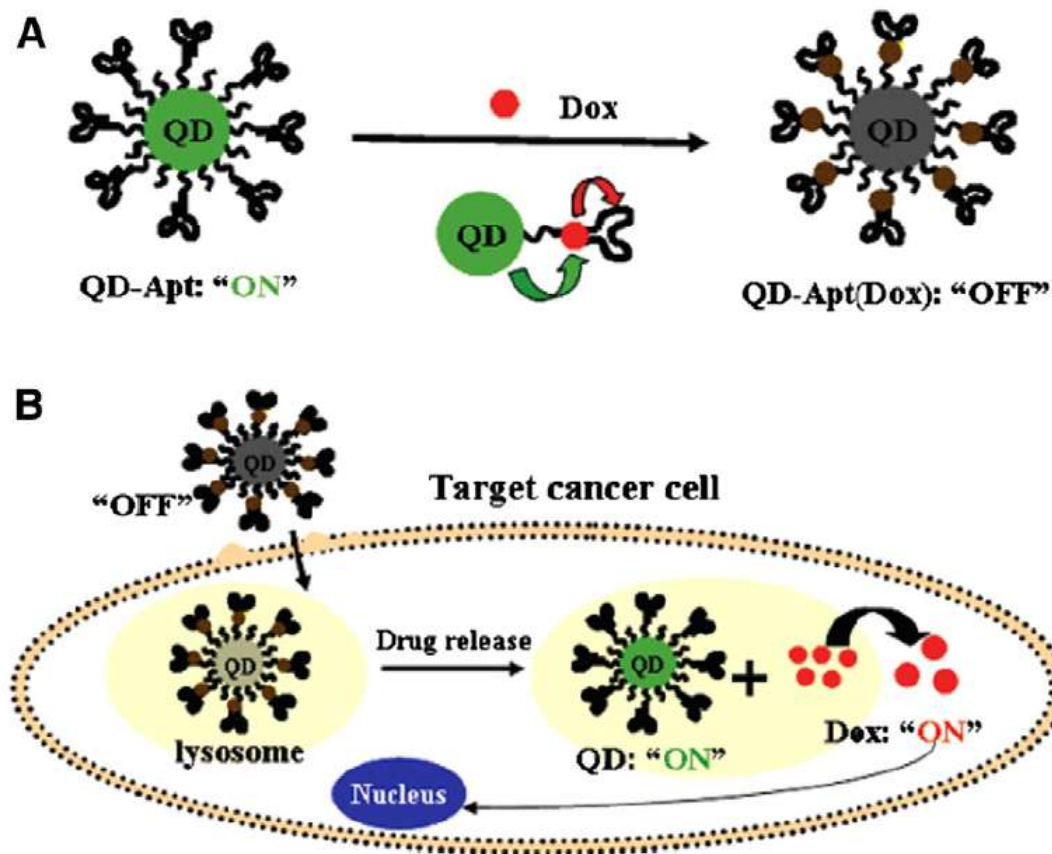
B.L Fay et al.

Int. J. Nanomedicine ,2015:10(1) p:6931—6941

### Photothérapie dynamique et délivrance

J.O. Durand et al.

International Journal of Pharmaceutics 2012, p505



Bagalkot V, et al. Quantum dot-aptamer conjugates for synchronous cancer imaging, therapy, and sensing of drug delivery based on bi-fluorescence resonance energy transfer. *Nano Lett* 2007; p:3065-70.



## Internalisation des nanoparticules :

- effet cytotoxique se traduit par une forte augmentation des ROS : radical hydroxyl  $\cdot\text{OH}$  and anions superoxides  $\cdot\text{O}_2^-$  and oxygen singulet  $^1\text{O}_2$ ,

- d'autres effets cytotoxiques peuvent aussi se manifester : oxydation  $\text{Ag}^0 \rightarrow \text{Ag}^+$  génotoxique par complexation sur les bases nucléiques (guanine et adénine)

$\text{Ag}^+$  catalyse l'oxydation de l'anion ascorbate dans la cellule produit une altération encore plus importante de l'ADN : **S.Valiyaveetil et al. ACS nano 2009 p279–290**

## **Comparison of the Abilities of Ambient and Manufactured Nanoparticles To Induce Cellular Toxicity According to an Oxidative Stress Paradigm** **Andre E. Nel et al. NANO LETTERS 2006 Vol. 6, No. 81794-1807**

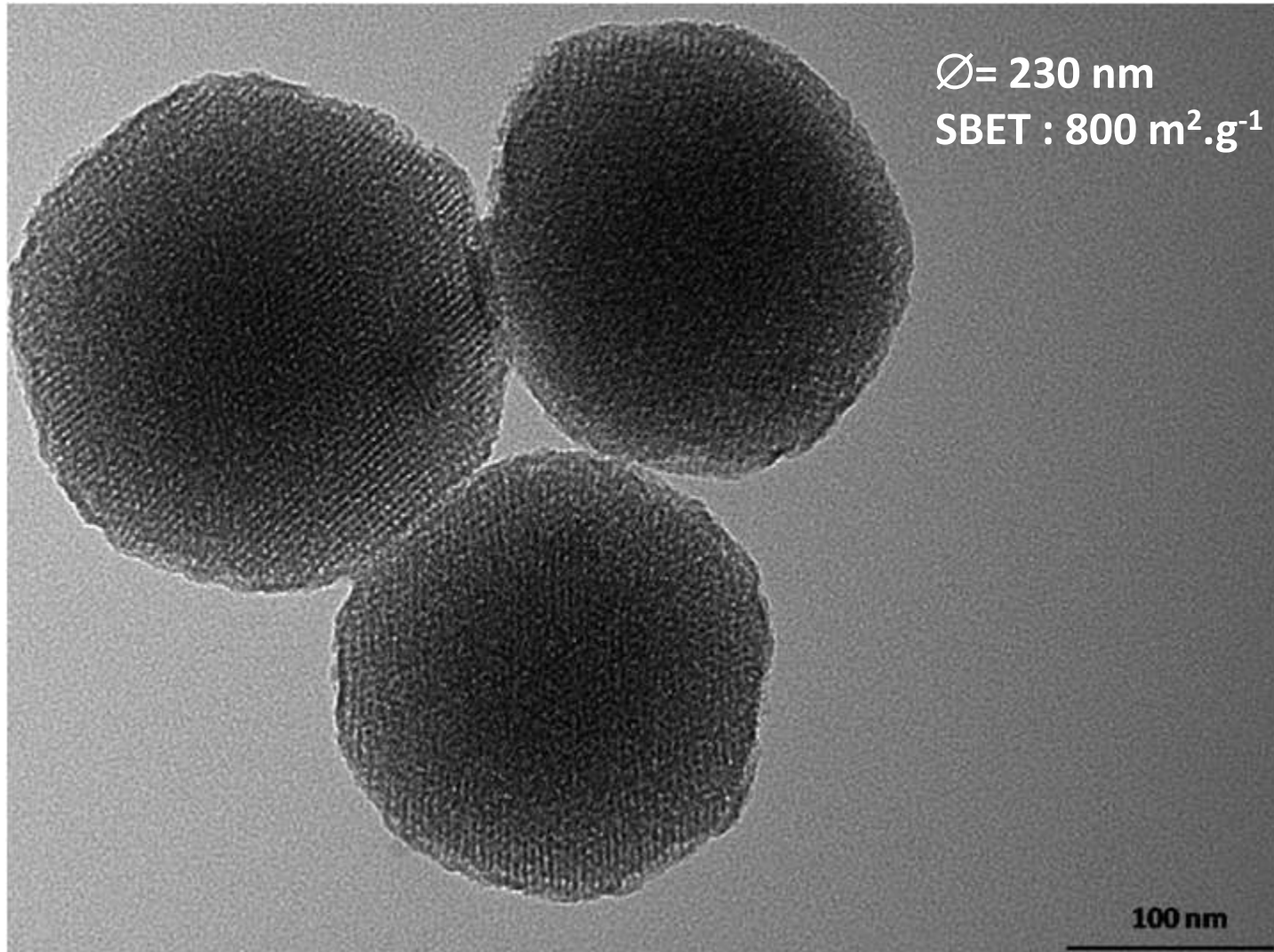
### ABSTRACT

**Nanomaterial properties differ from those bulk materials ...** A possible downside of these capabilities is **harmful interactions with biological systems, with the potential to generate toxicity**. An approach to assess the safety of nanomaterials is urgently required. We compared the cellular effects of ambient ultrafine particles with manufactured titanium dioxide ( $\text{TiO}_2$ ), carbon black, and.... The study was conducted in a phagocytic cell line (RAW 264.7) that is representative of a lung target for NPs.. Particles differed with respect to cellular uptake, subcellular localization, and ability to catalyze the production of reactive oxygen species (ROS) under biotic and abiotic conditions. Spontaneous ROS production was compared by using an ROS quencher (furfuryl alcohol) as well as an NADPH peroxidase bioelectrode platform. Among the particles tested, ambient ultrafine particles (UFPs) and cationic PS nanospheres were capable of inducing cellular ROS production, GSH depletion, and toxic oxidative stress. **This toxicity involves mitochondrial injury through increased calcium uptake and structural organellar damage.**

In summary, we demonstrate that ROS generation and oxidative stress are a valid test paradigm to compare NP toxicity. **Although not all materials have electronic configurations or surface properties to allow spontaneous ROS generation, particle interactions with cellular components are capable of generating oxidative stress.**

## Couplage d'antioxydant à la surface des nanoparticules : limiter le stress oxydant

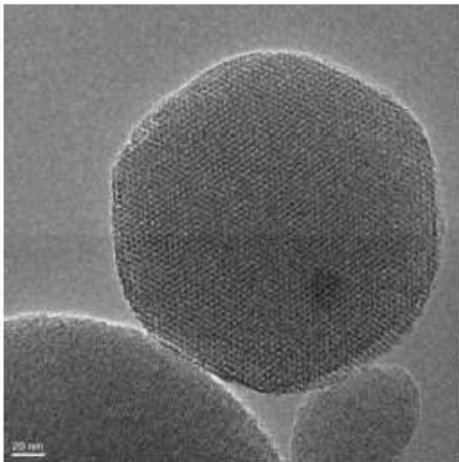
L'étude a été réalisée sur des nanotransporteurs de type silice MSN :



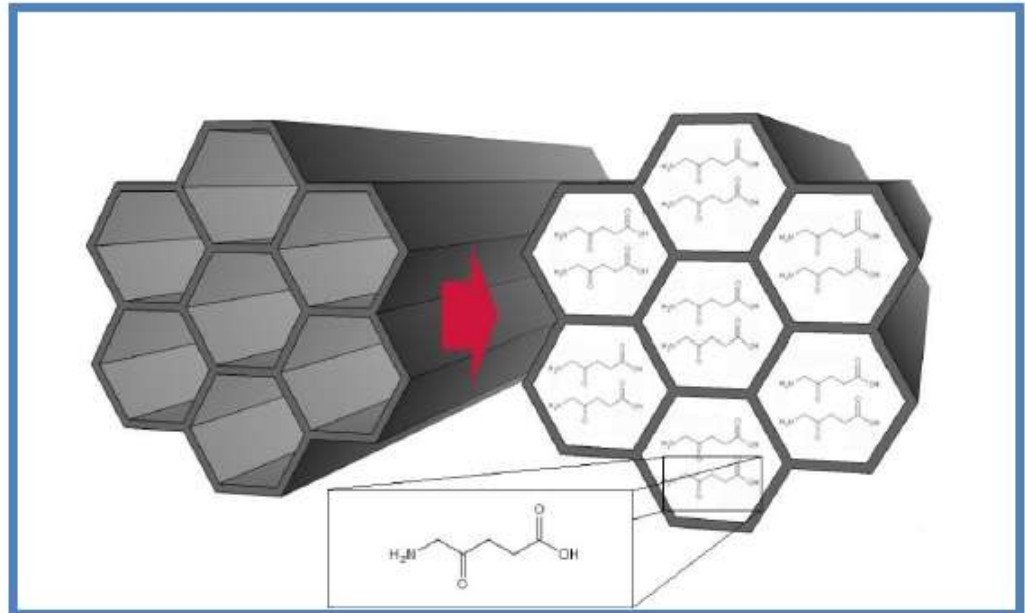
## Nombreuses Spécificités :

- Volume poreux et surface spécifique élevée autorise un chargement important de molécules bioactives
- une libération par diffusion contrôlée par l'organisation de la porosité (hexagonale, radiale, désordonnée...)
- Bonne stabilité chimique
- Biocompatible et peu toxique
- **Surfaces facilement fonctionnalisées** par greffage chimique (groupement Si-OH)

M. Vallet-Regí et al. Angew. Chem. Int. Ed. 2007

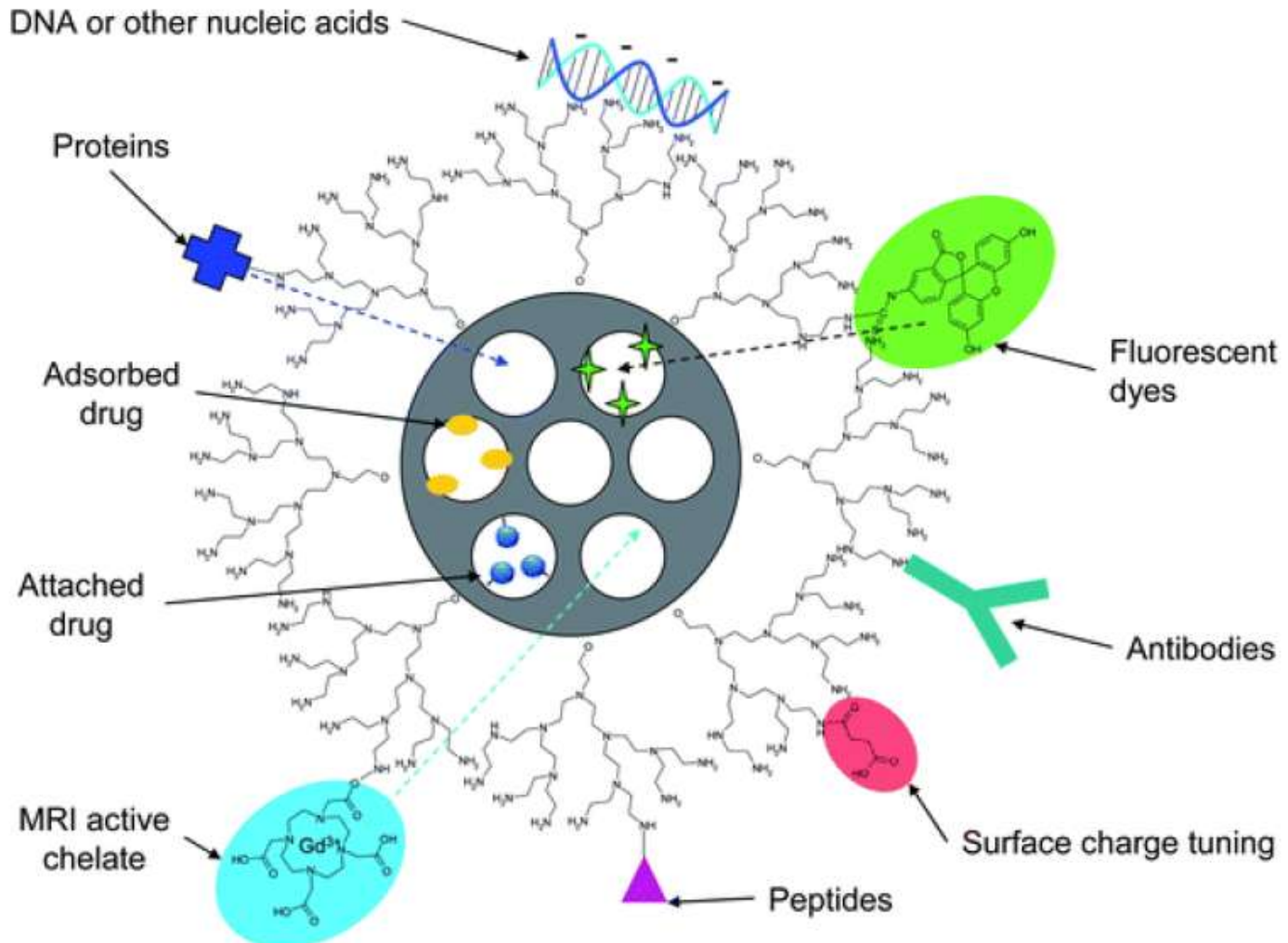


Mesoporous silica nanoparticles (MSN)



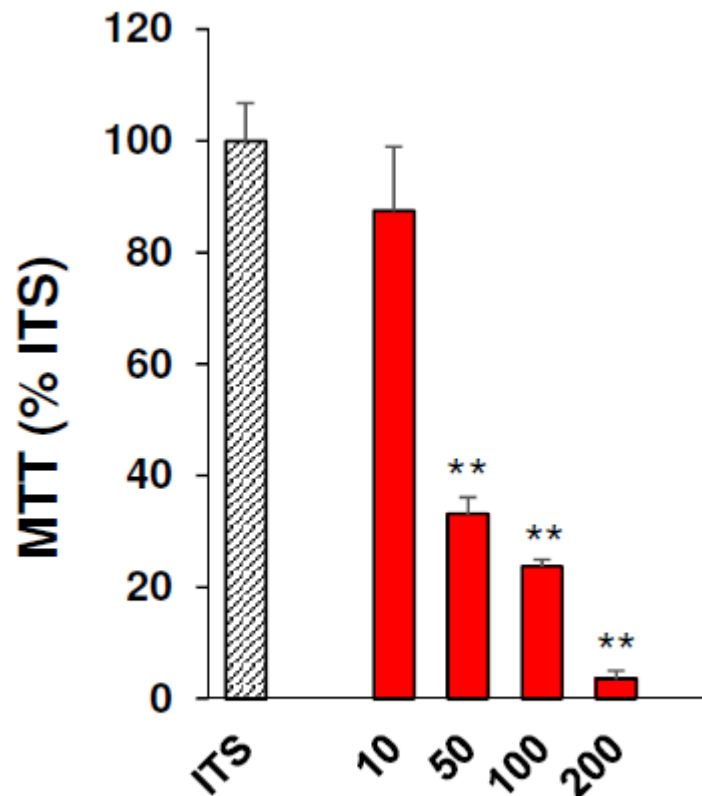


## Plateformes très versatiles

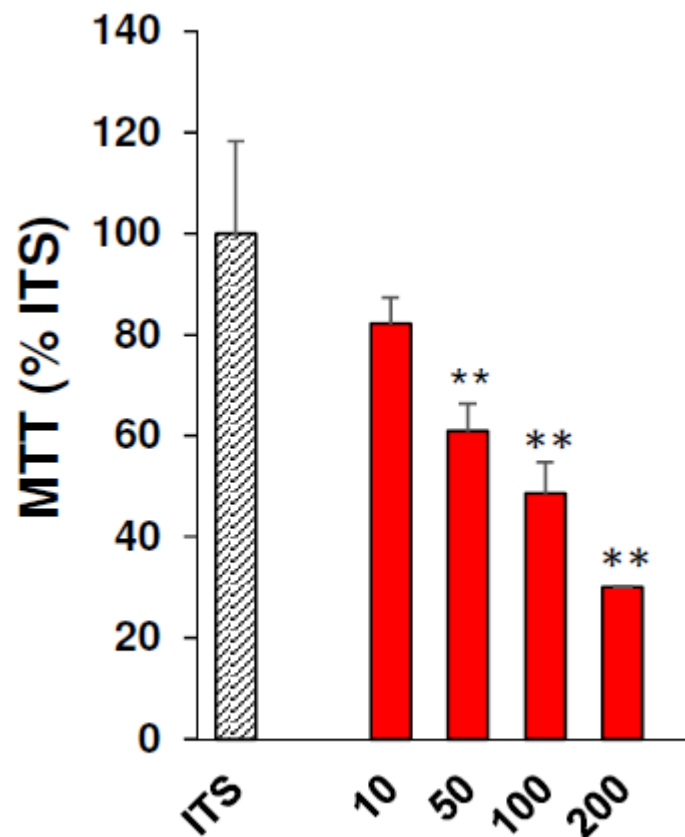


## 2 barrières à l'absorption des nanoparticules : la peau et l'intestin

Cellules HACAT

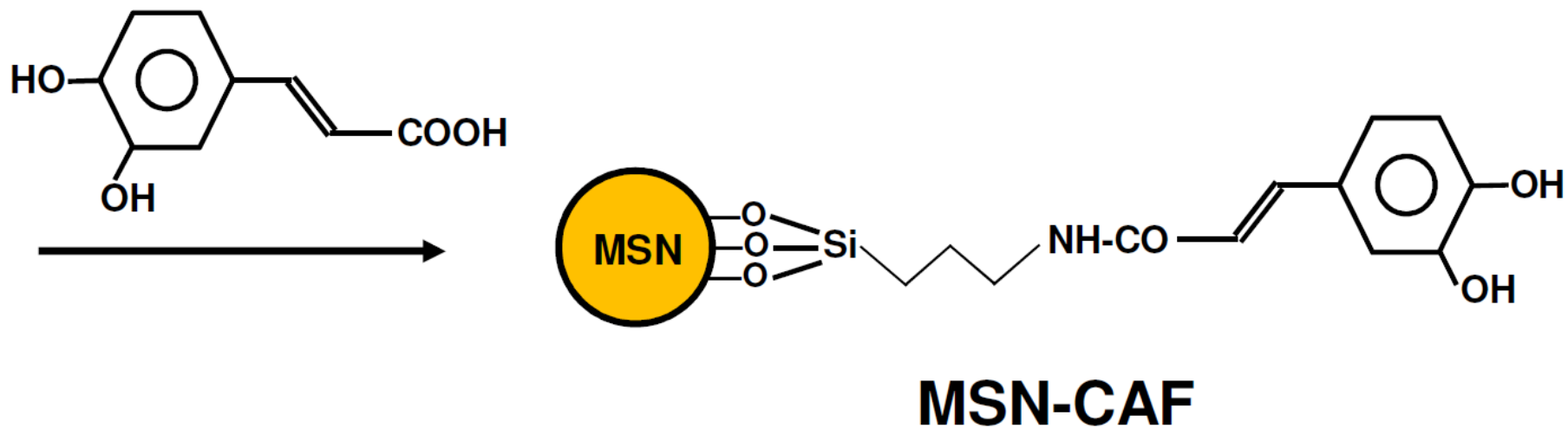
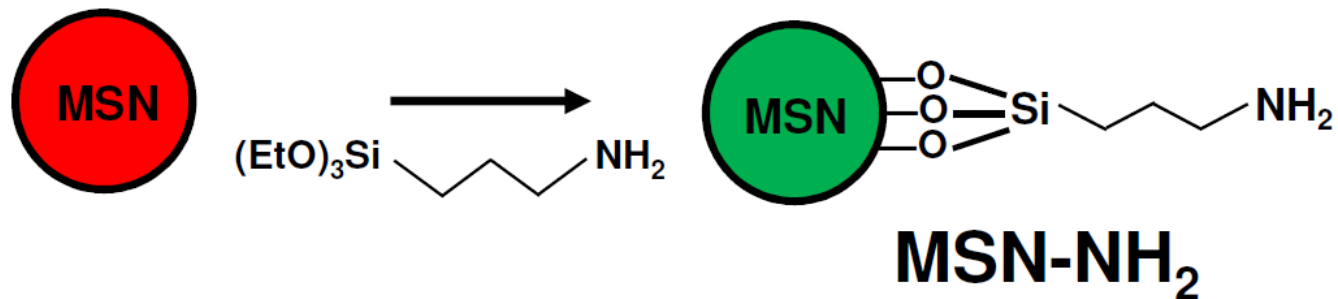


Cellules Caco2



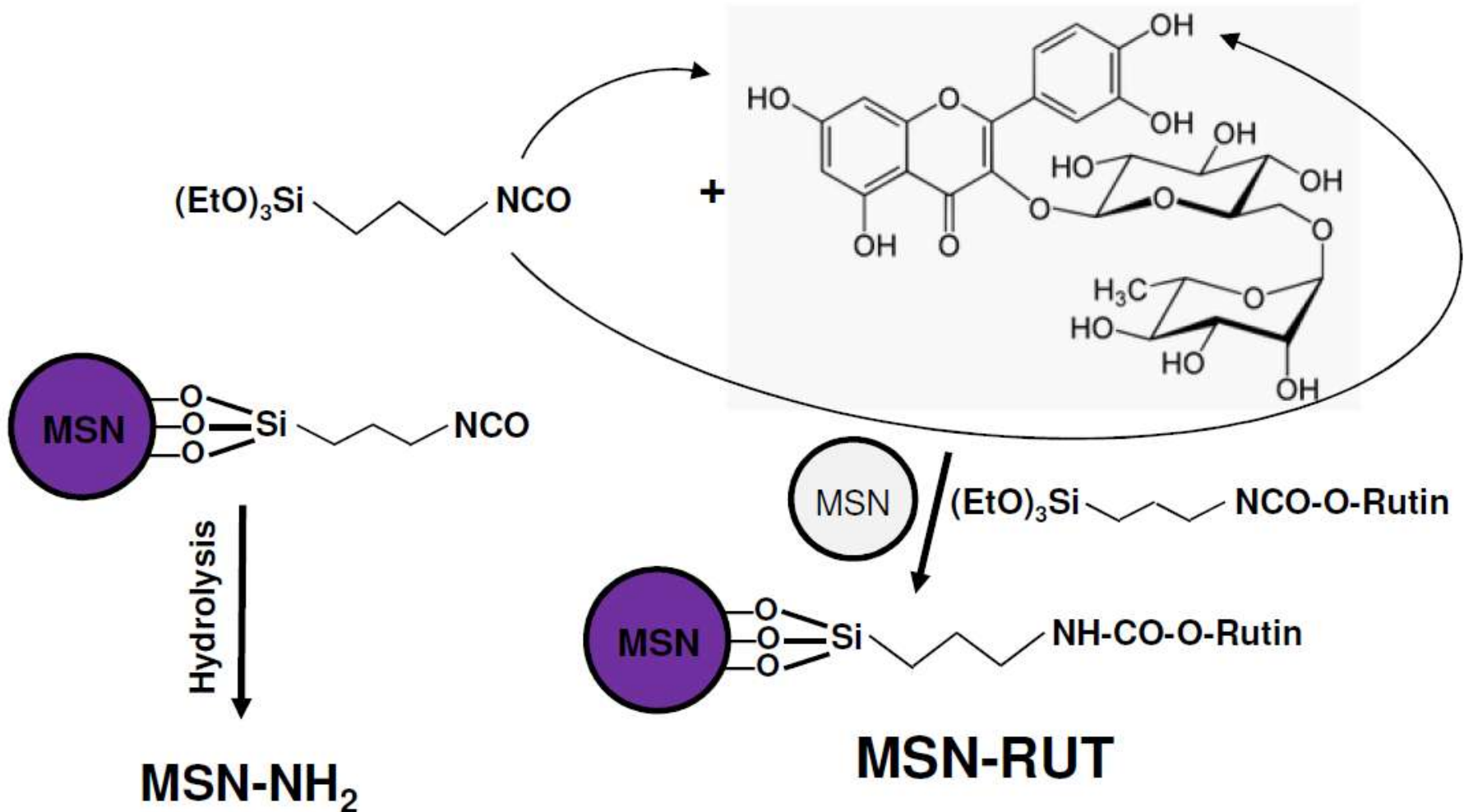


## Functionalization of MSNs with caffeic acid.



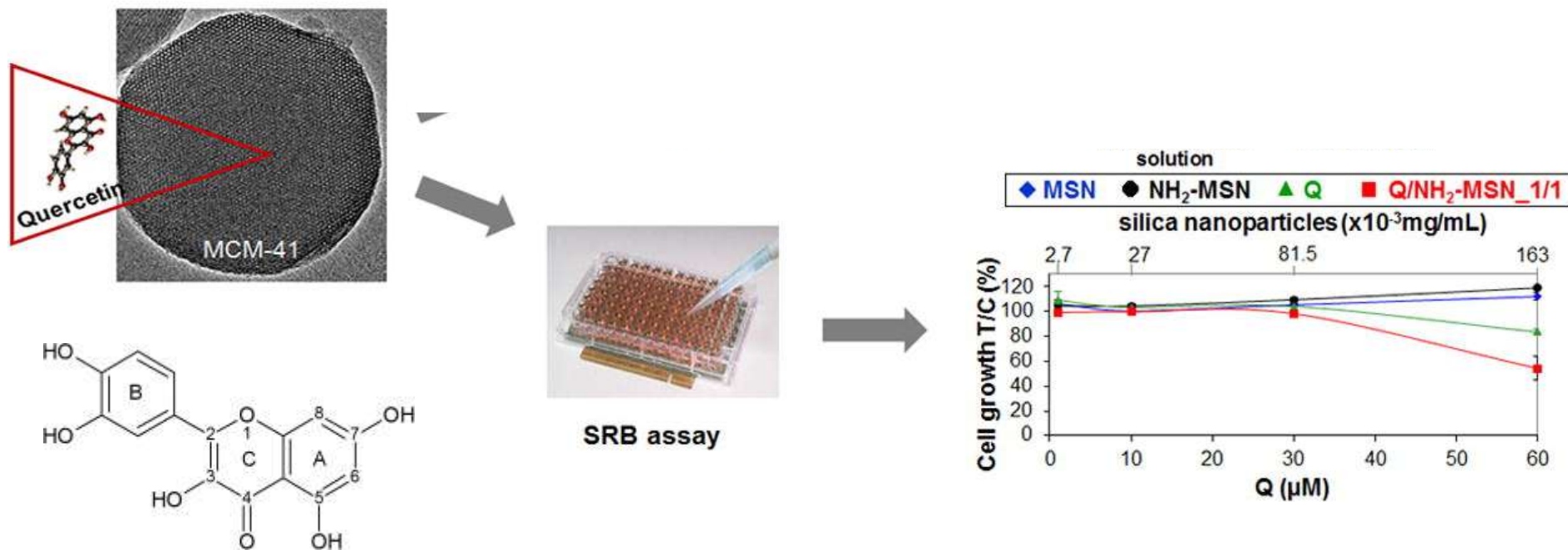
4.4  $\mu\text{mol}/\text{mg}$  de particules

## Functionalization of MSNs with rutin.



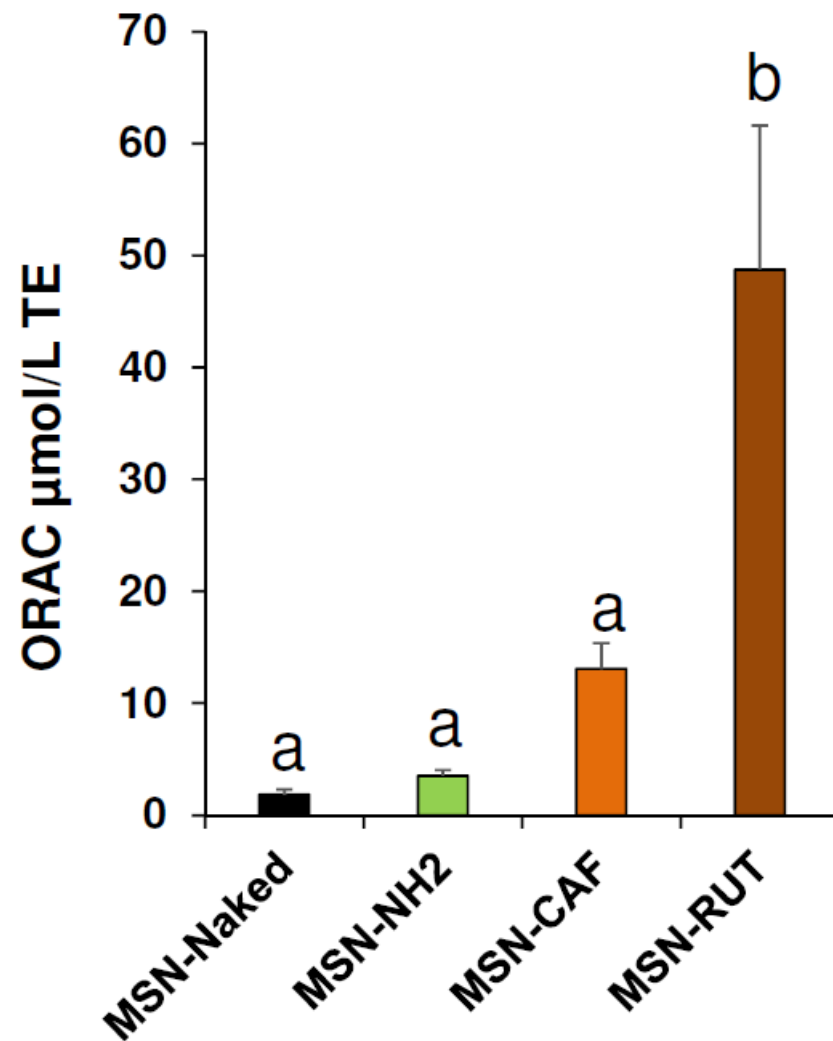
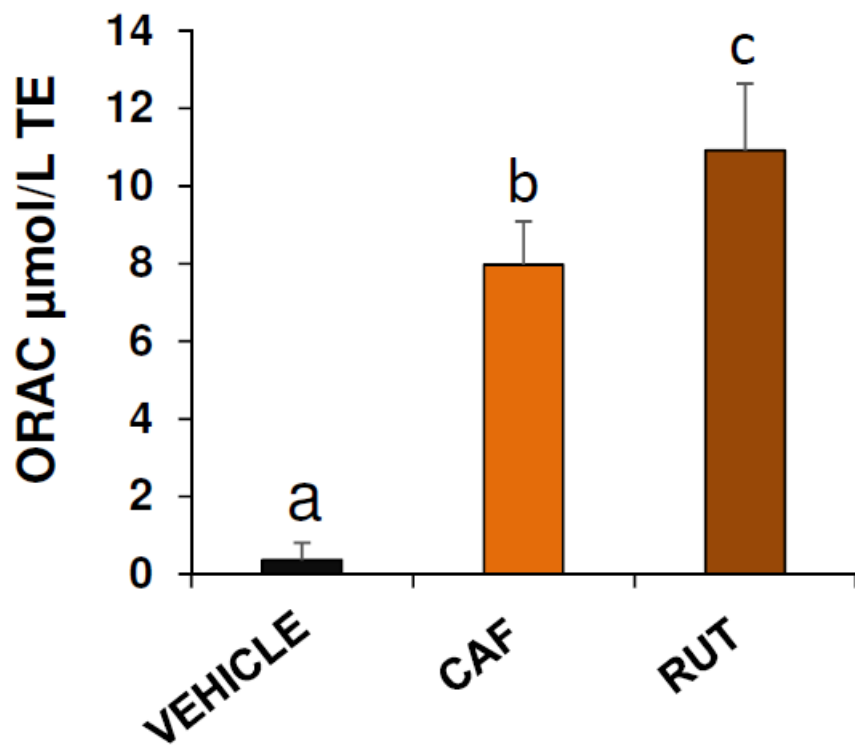
0.22  $\mu\text{mol}/\text{mg}$  de particules

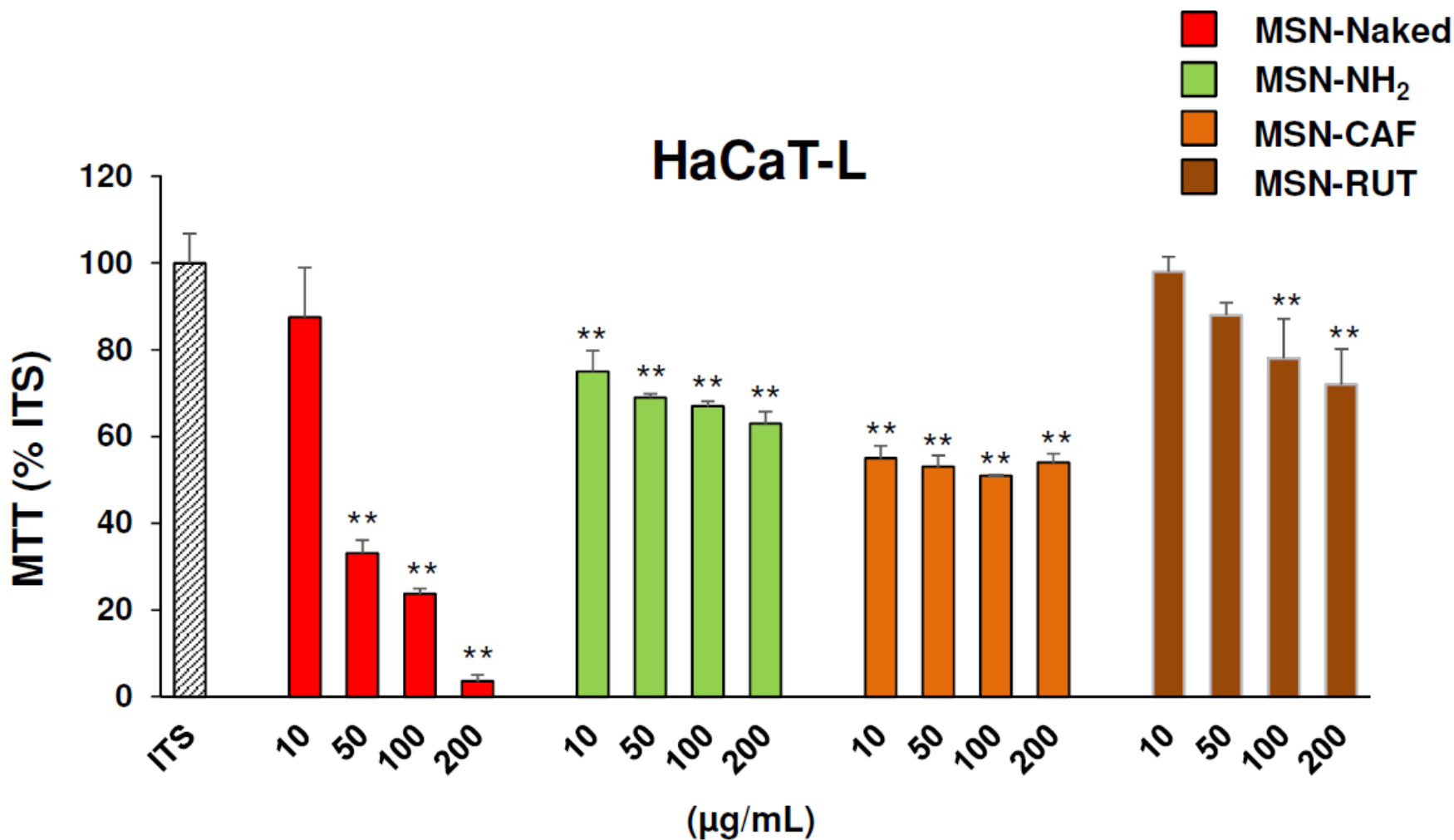
**Mesoporous silica as topical nanocarriers for quercetin: characterization and *in vitro* studies : S. Oliaro-Bossoa et al. European Journal of Pharmaceutics and Biopharmaceutics , 2015, p 116–125**

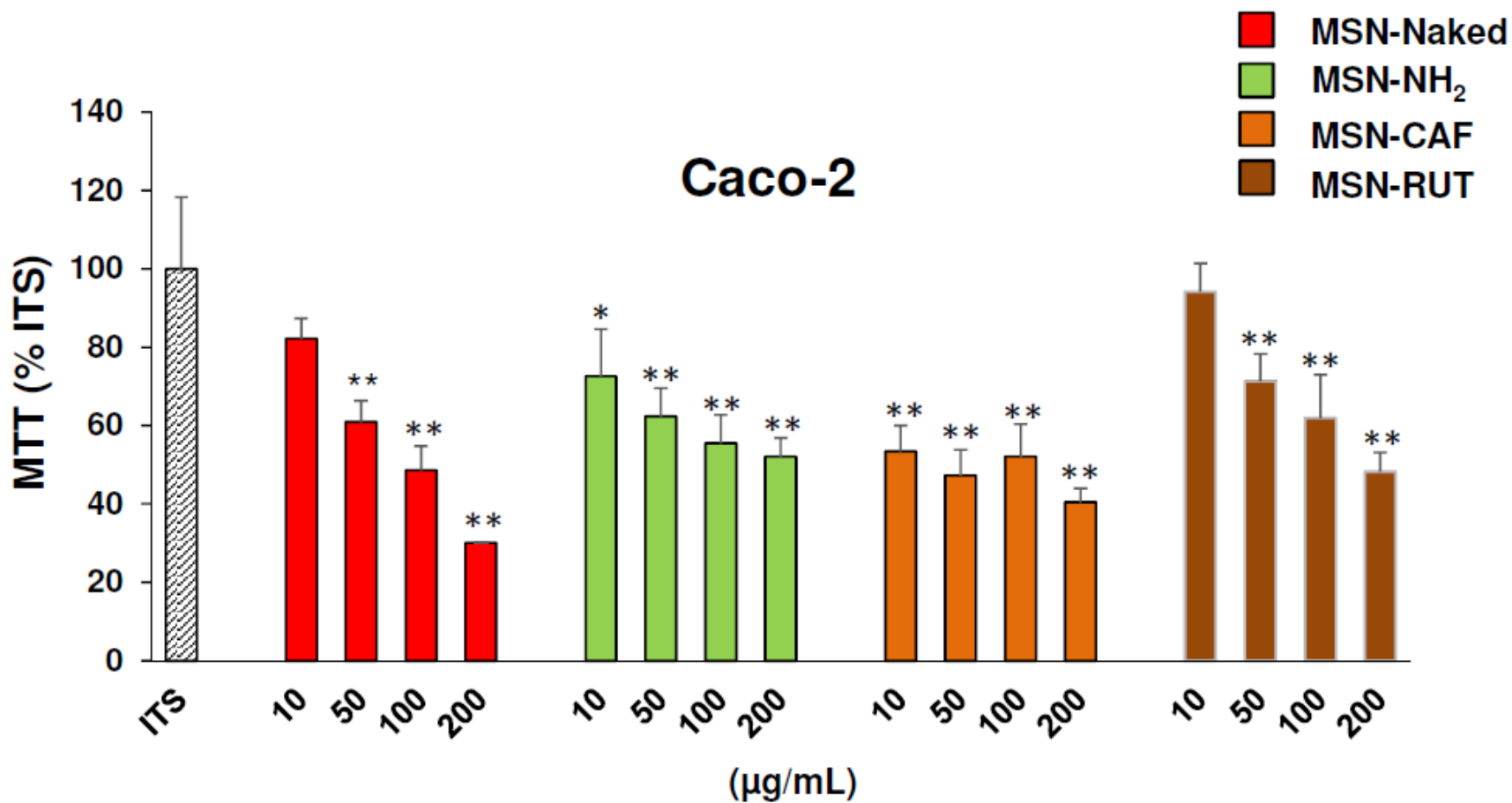


At a concentration 60 μM the complex with NH<sub>2</sub>-MSN was more effective than quercetin alone, causing about 50% inhibition of cell proliferation (JR8 human melanoma cells).

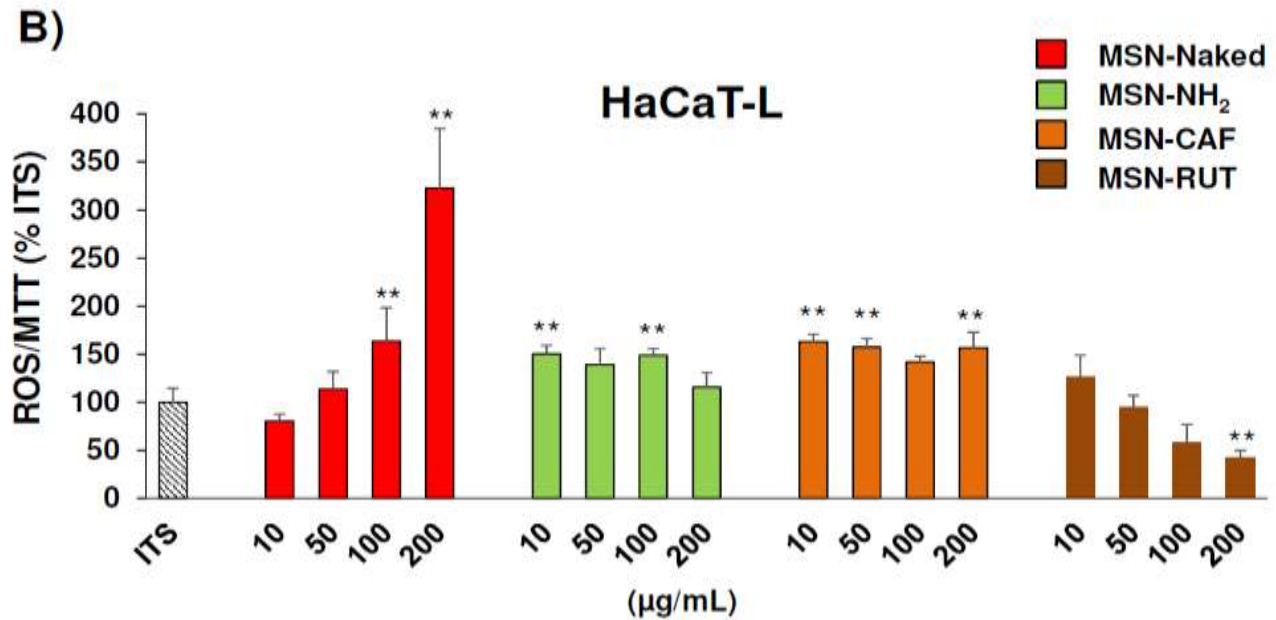
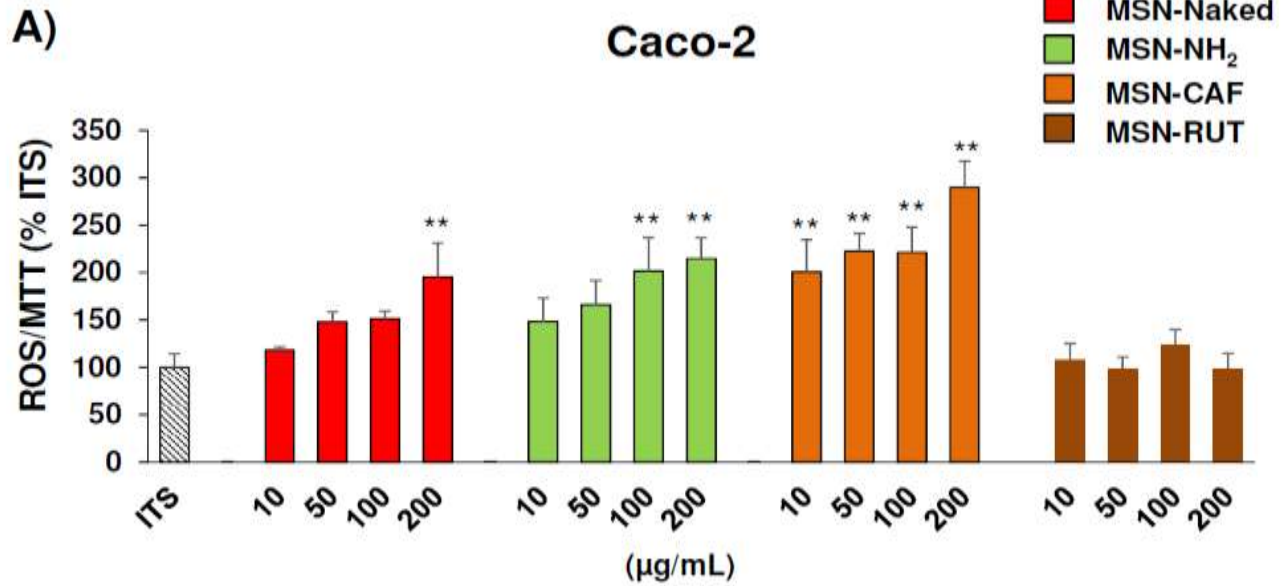




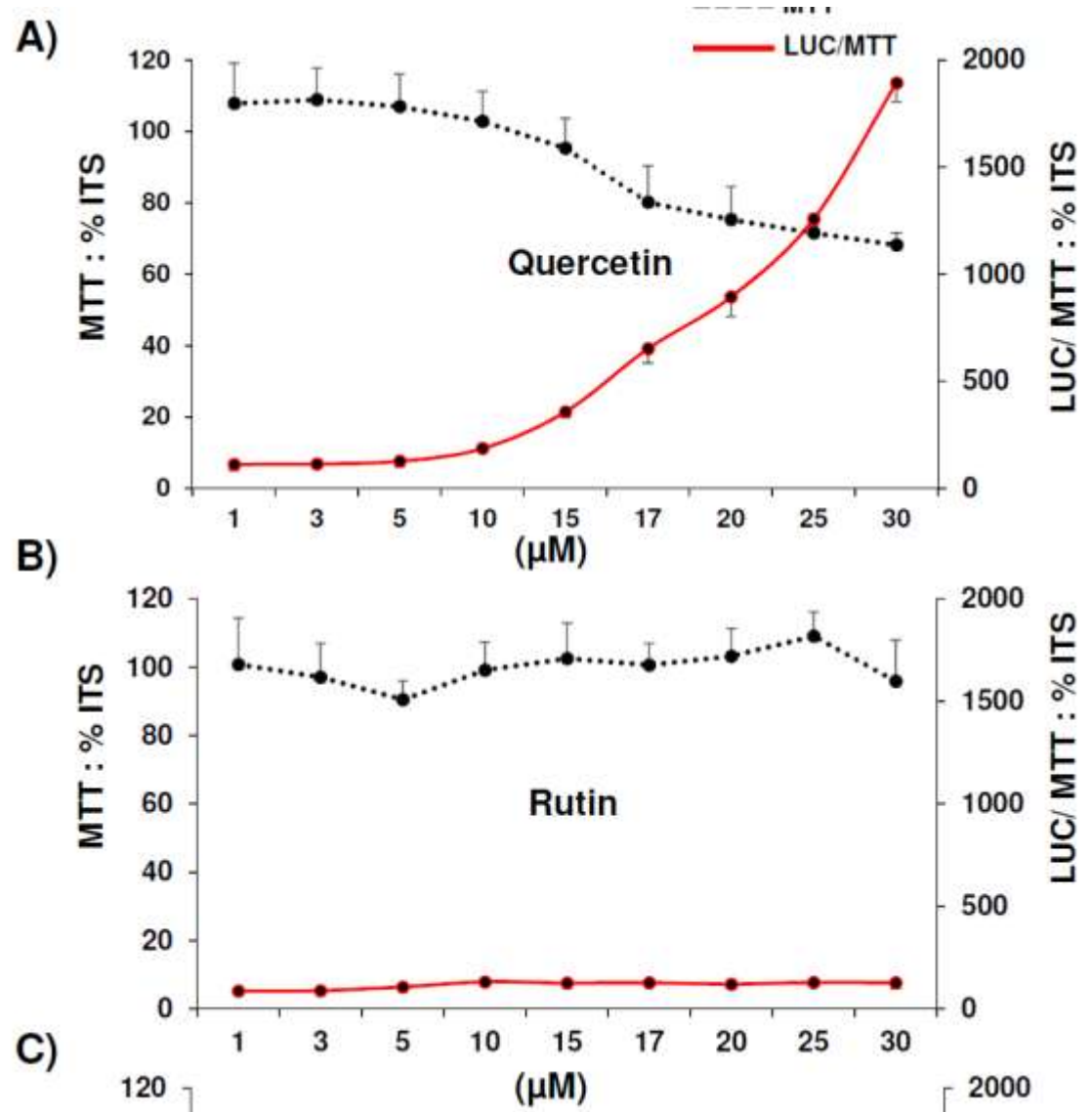


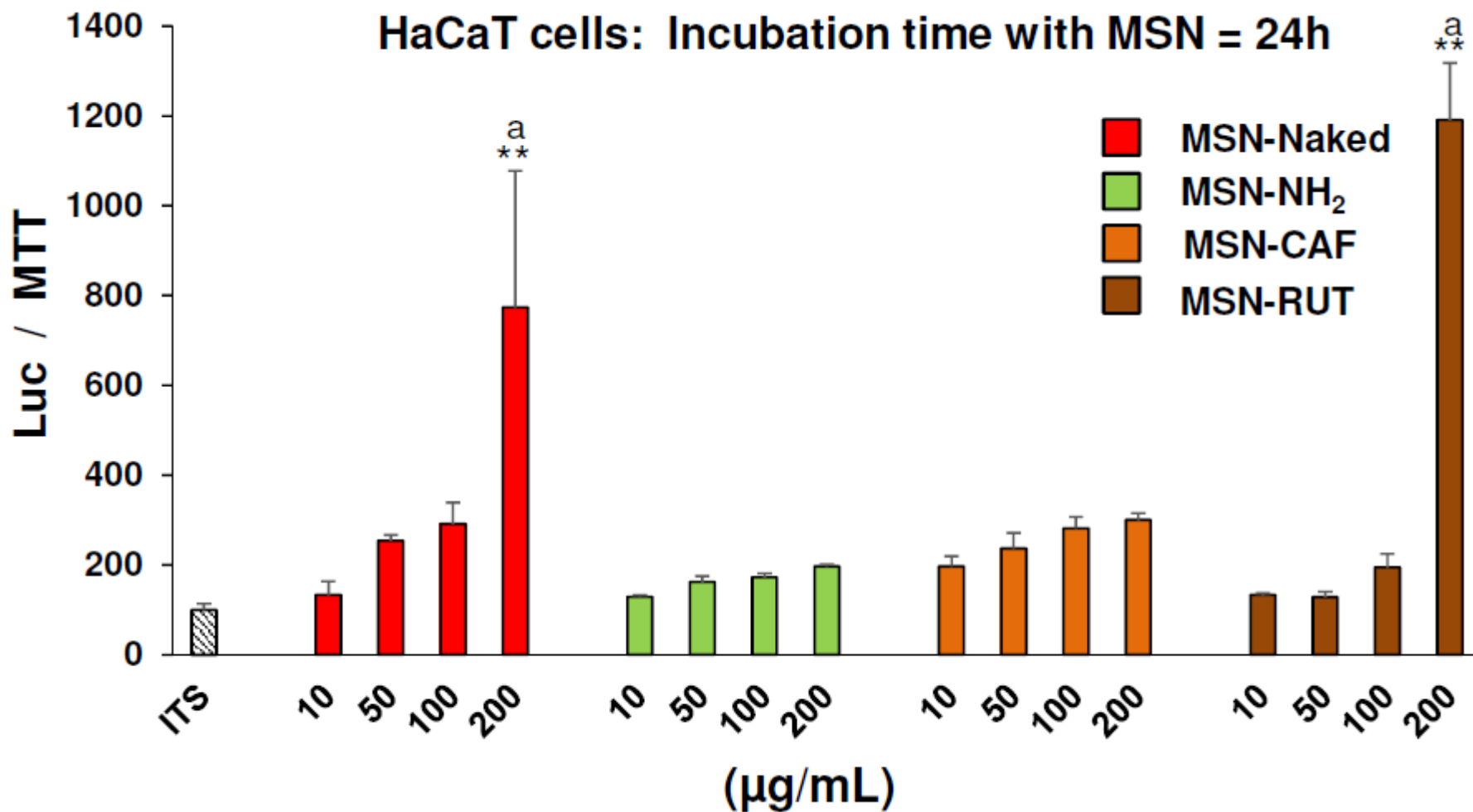






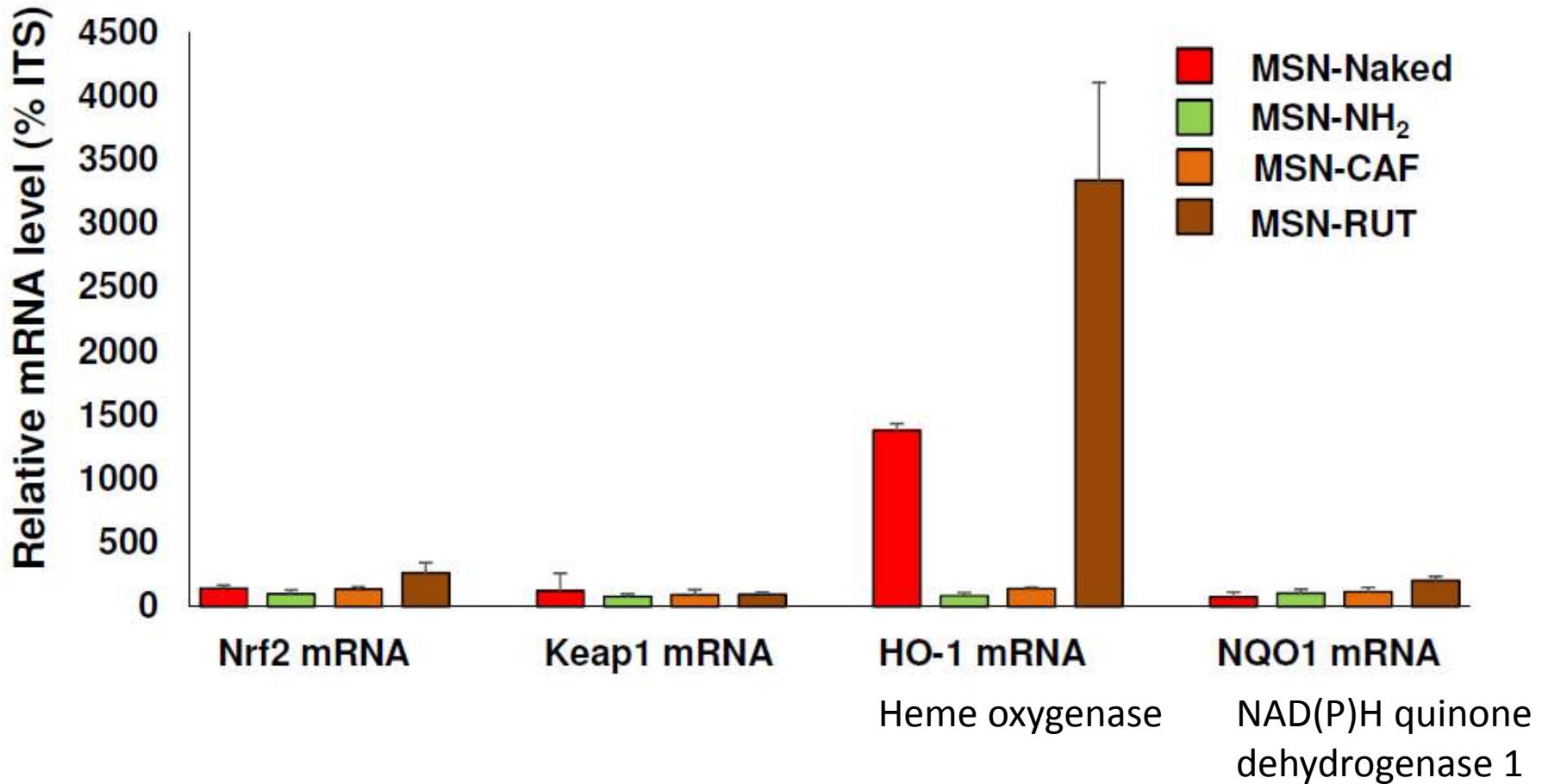
**Cellules HaCaT transfectées par un plasmide avec 8 ARE placés devant le gène de la luciférase**  
**Lignée cellulaire fournie par Patrick Balaguer (DR INSERM à l'IRCM)**  
**Activation de la voie Nrf2 induit la luciférase : luminescence proportionnelle à l'intensité de l'activation de la voie Nrf2**



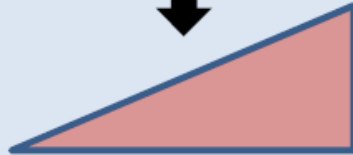




HaCaT cells: Incubation time with 200 µg/ml MSN = 24h

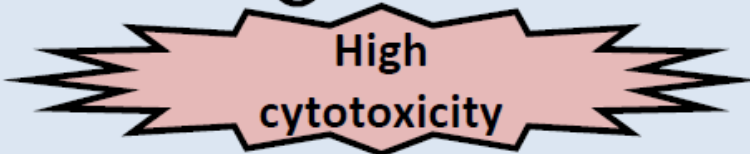


**MSN-Naked**



High level of ROS

① ↓



High cytotoxicity

② ↓

↑ Nrf2 pathway (inefficient)

③ ↓

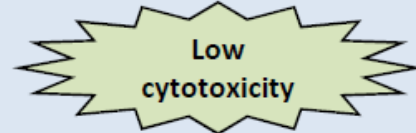
**Cellular death**

**MSN-RUT**



Low level of ROS

④ ↓



Low cytotoxicity

⑤ ↓

↑ Nrf2 pathway (efficient)

⑥ ↓

**Cytoprotection**

**HaCAT Cell**

Je vous remercie de  
votre attention

**CHEMISTRY: MOLECULES TO MATERIALS**