



# Stratégie thérapeutique de l'hépatocarcinome (CHC) : pertinence de la vectorisation ?

Flavien Delaporte sous la direction du Dr Camille Savary

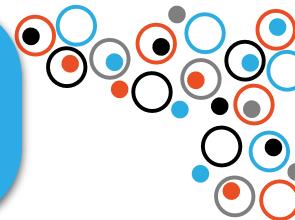
Présidente : Mme Catherine Passirani-Malleret  
Directrice : Mme Camille Savary  
Membre : Mr Jérôme Boursier  
Membre : Mr Gaël Le Roux  
Membre : Mr Matthew Burbank

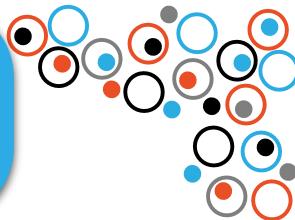
## Contexte CHC

## Les nanoparticules

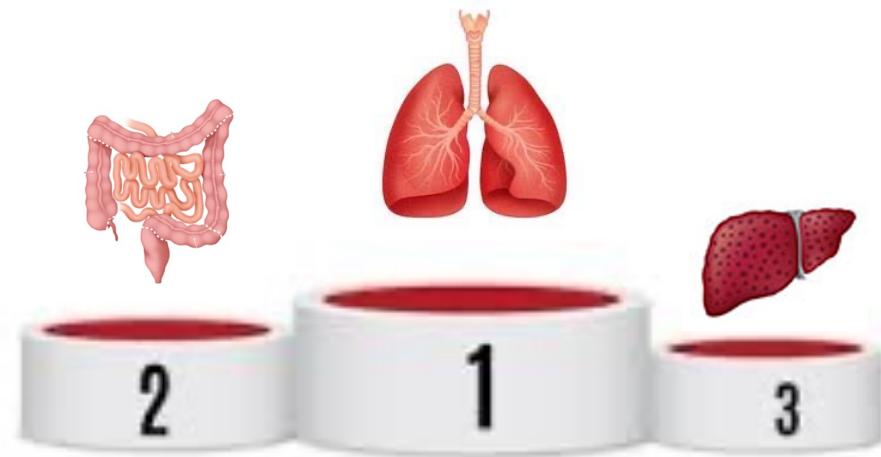
## Étude préliminaire

## Conclusion

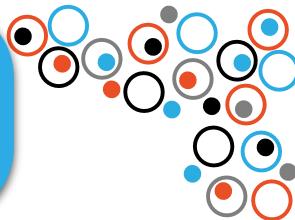




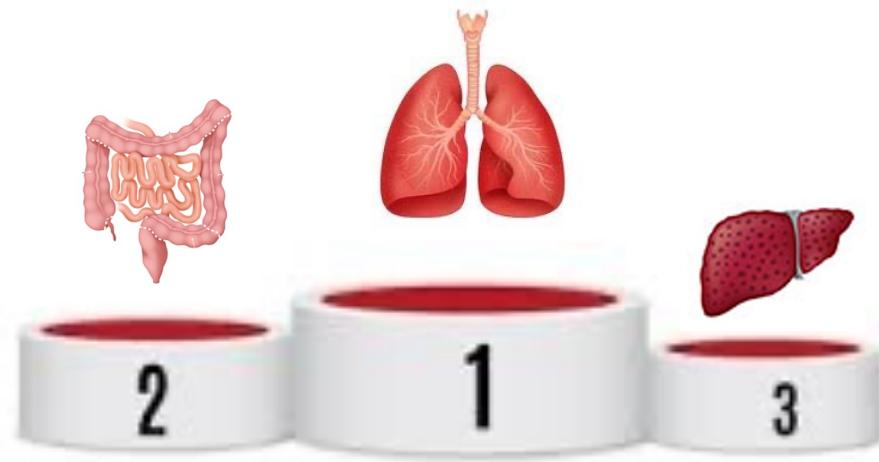
### Létalité parmi les cancers



906 000 nouveaux cas / an  
830 000 décès / an  
 $\text{Incidence}_{\text{hommes}} > \text{Incidence}_{\text{femmes}}$



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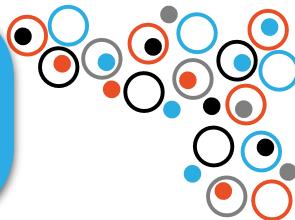
**Problème de santé publique majeur**

## Contexte Épidémiologie

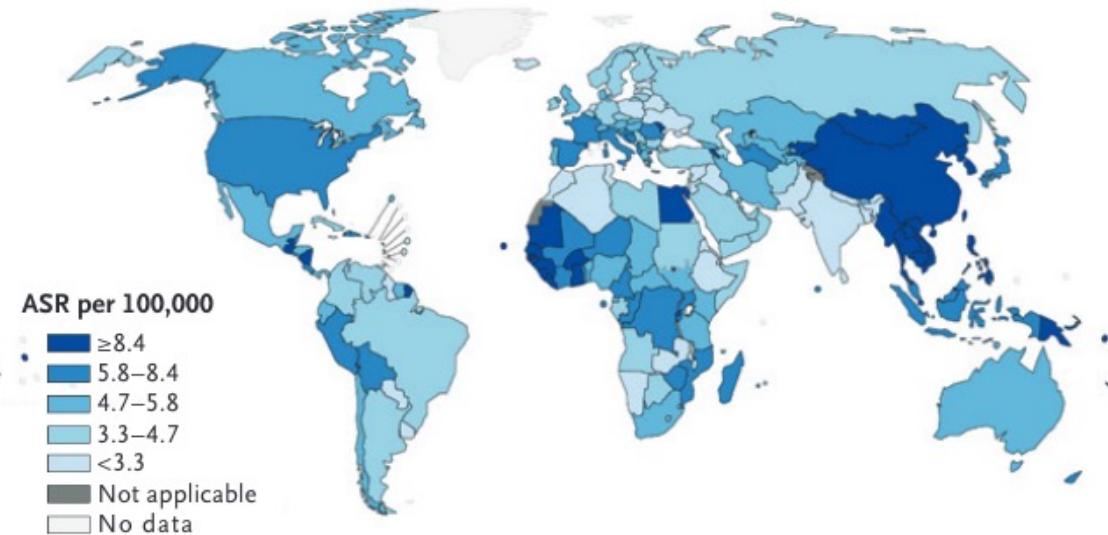
## Les nanoparticules

## Étude préliminaire

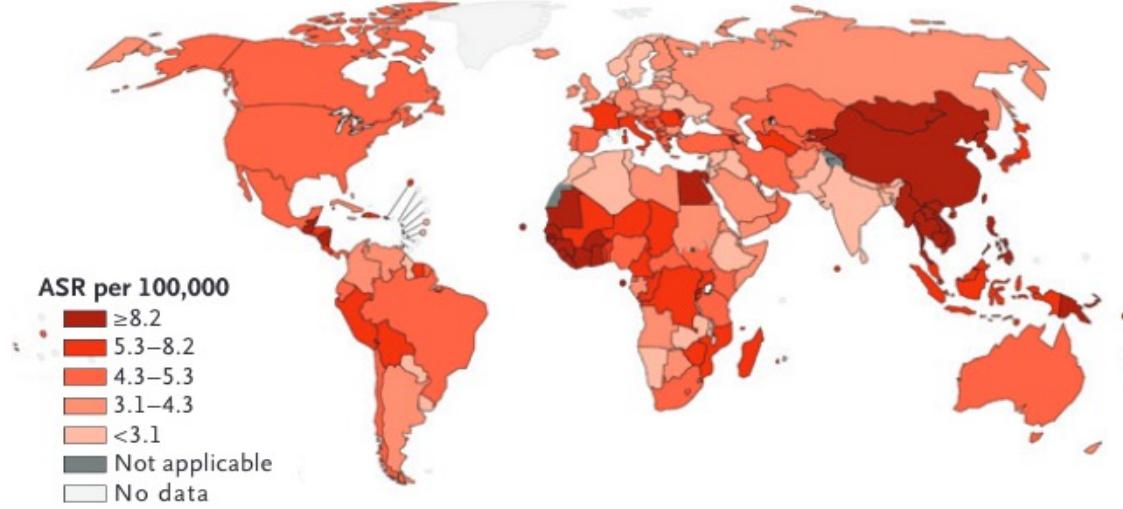
## Conclusion



Incidence



Mortalité



Disparités d'incidence et de mortalité → **Accès aux traitements** & facteurs étiologiques

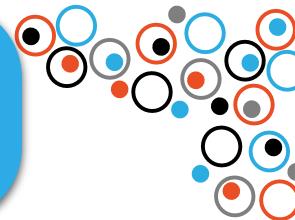
Augmentation CHC dans les pays développés à économie de marché due aux facteurs de risques +++  
(diabète, obésité, alcool)

## Contexte Facteurs de risque

## Les nanoparticules

## Étude préliminaire

## Conclusion



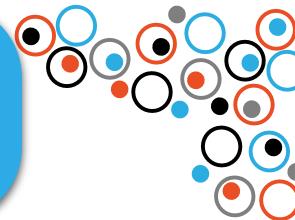
Hépatocarcinome

## Contexte Facteurs de risque

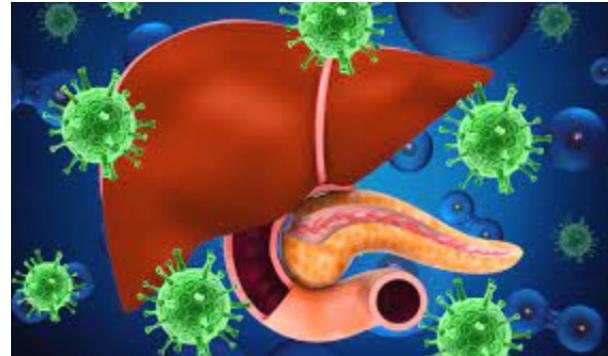
## Les nanoparticules

## Étude préliminaire

## Conclusion



Hépatites virales (VHB/VHC)



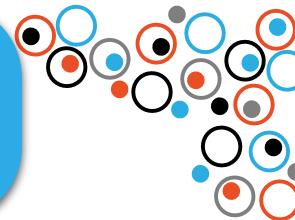
Hépatocarcinome

## Contexte Facteurs de risque

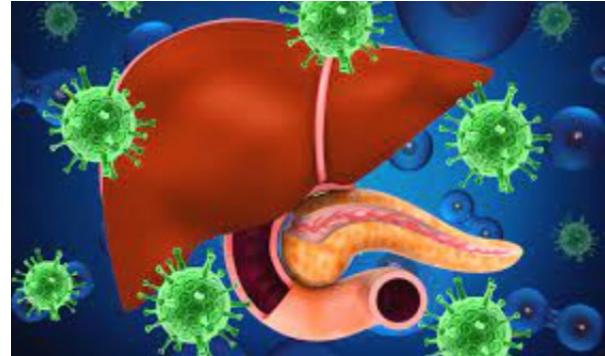
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## Étude préliminaire

## Conclusion



Hépatites virales (VHB/VHC)



Hépatocarcinome

Alcool

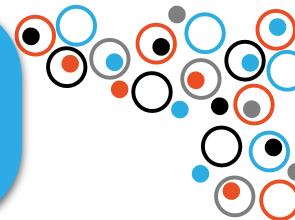


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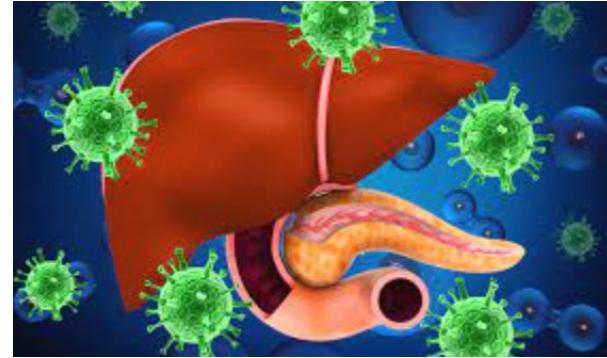
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## Étude préliminaire

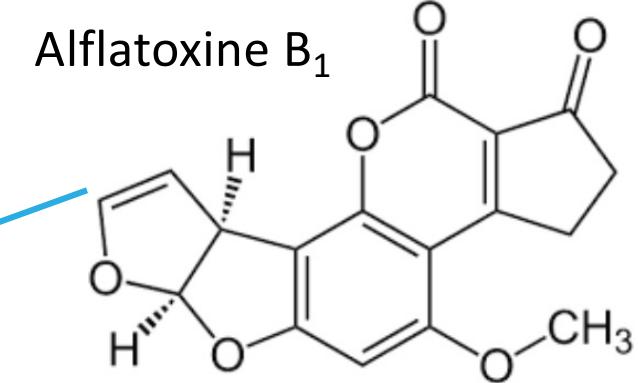
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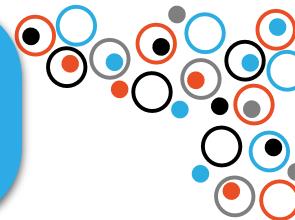


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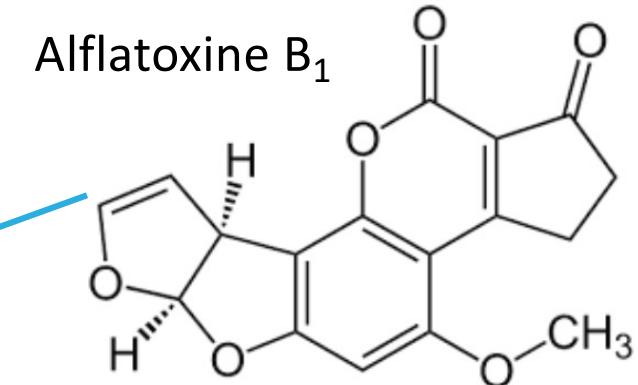
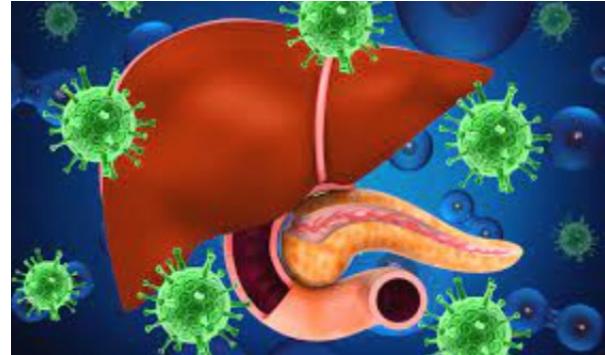
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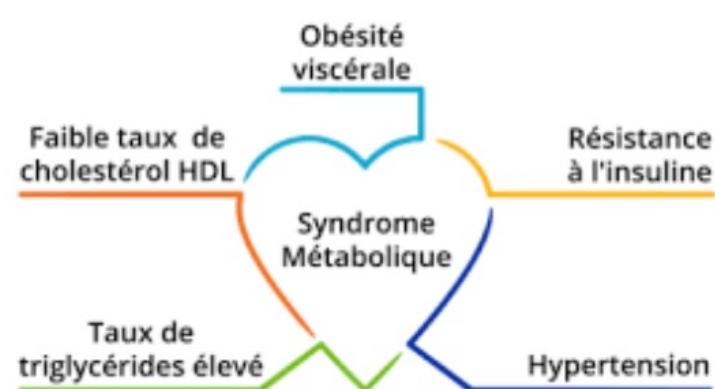
## Conclusion



### Hépatites virales (VHB/VHC)



### Hépatocarcinome



### Alcool

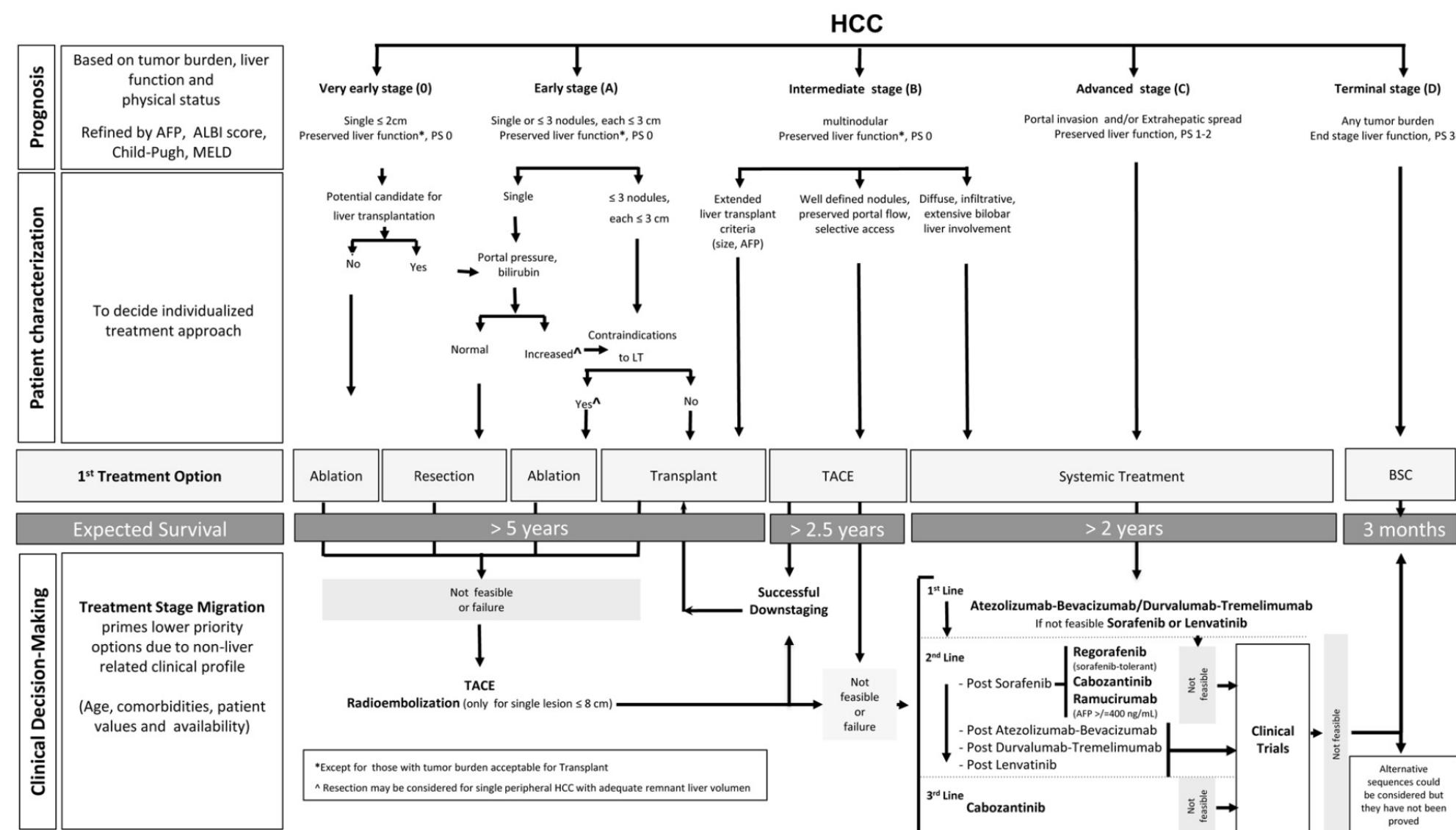


## Contexte Prise en charge

## Les nanoparticules

## Étude préliminaire

## Conclusion

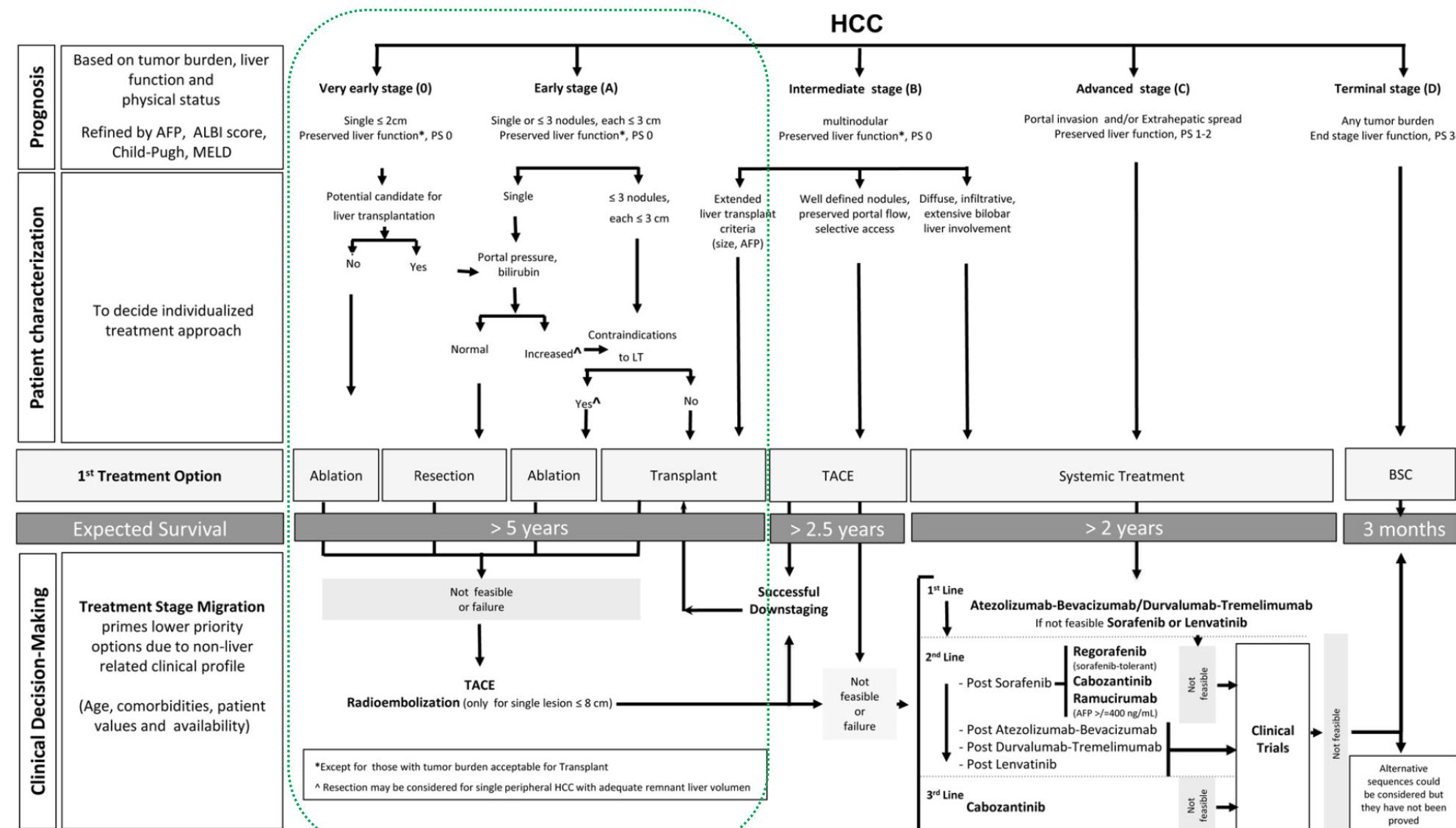


## Contexte Prise en charge

## Les nanoparticules

## Étude préliminaire

## Conclusion

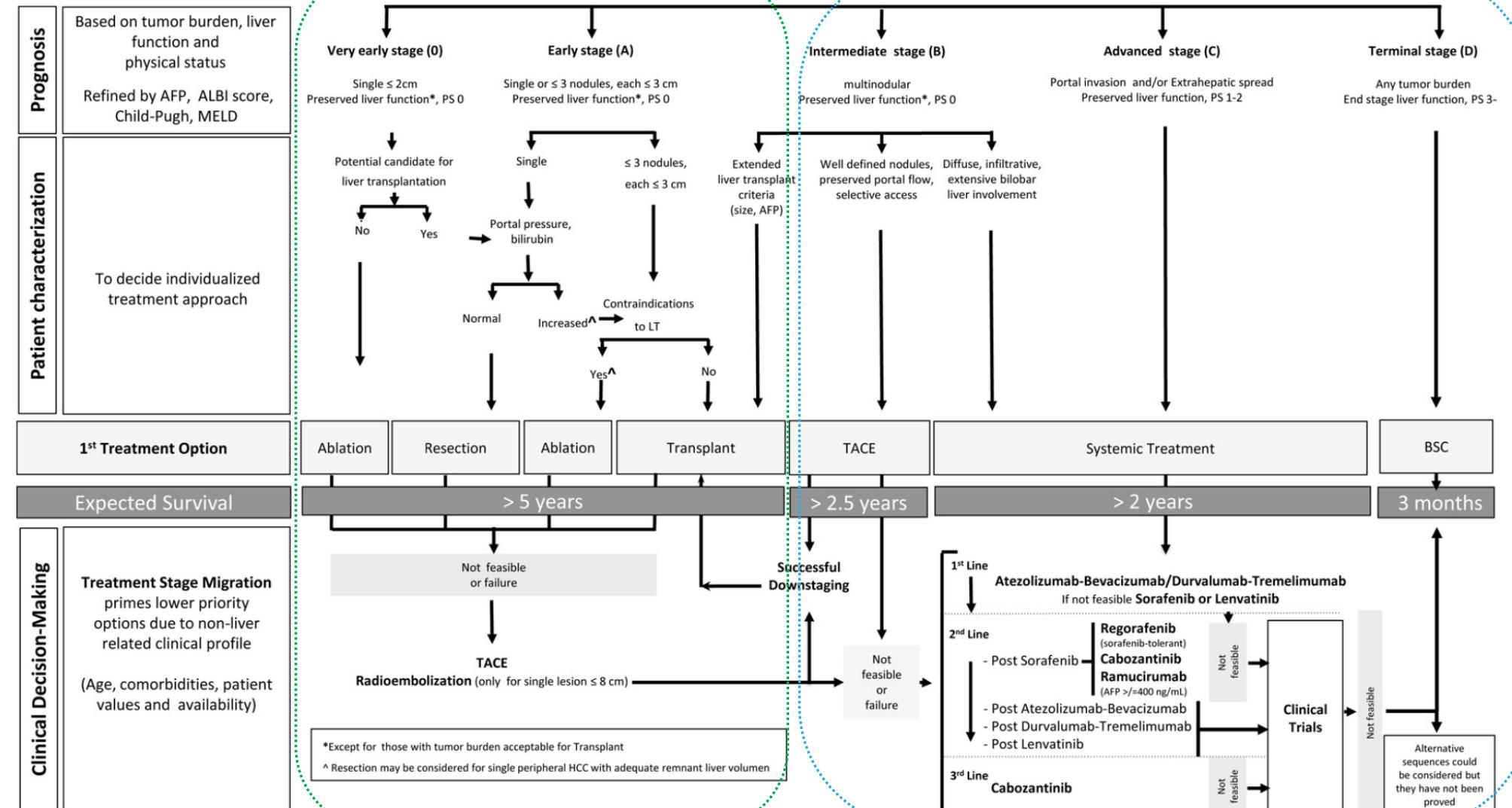


## Contexte Prise en charge

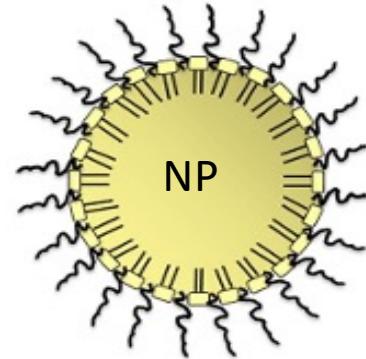
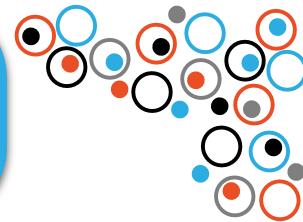
## Les nanoparticules

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## Conclusion



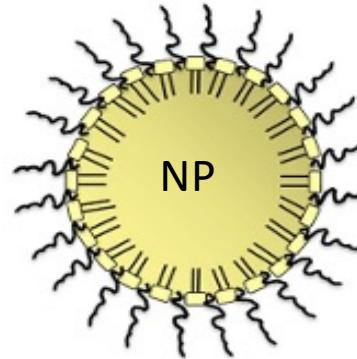
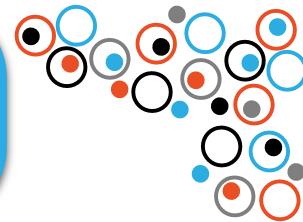
## OBJECTIF DE LA THÈSE



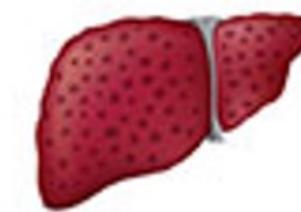
Intérêt dans le traitement du CHC ?



## OBJECTIF DE LA THÈSE



Intérêt dans le traitement du CHC ?



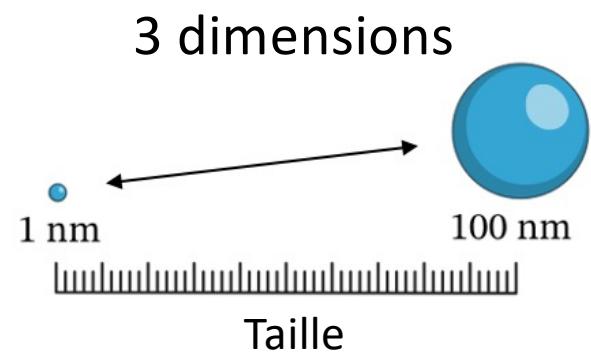
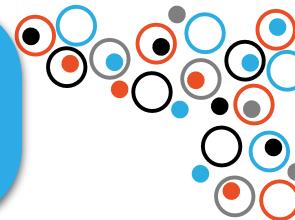
- Avantages NCL vs. formulations classiques (littérature)
- Preuve du concept (étude préliminaire)
  - Données de toxicité/biocompatibilité
  - Données cinétiques

Contexte

## Les nanoparticules Introduction

Étude préliminaire

Conclusion

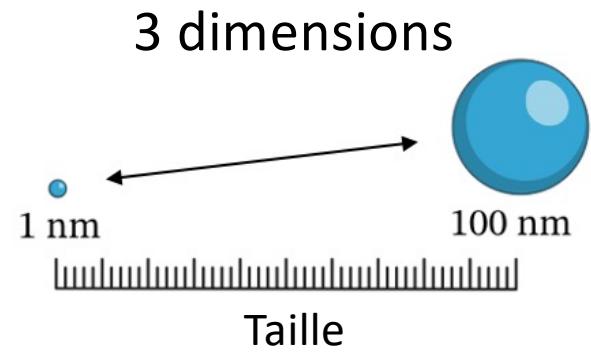
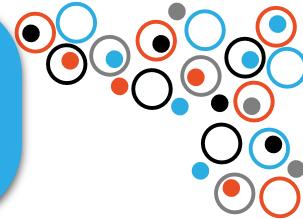


Contexte

## Les nanoparticules Introduction

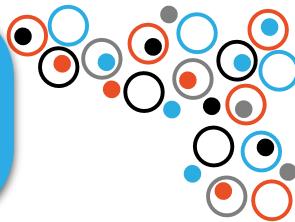
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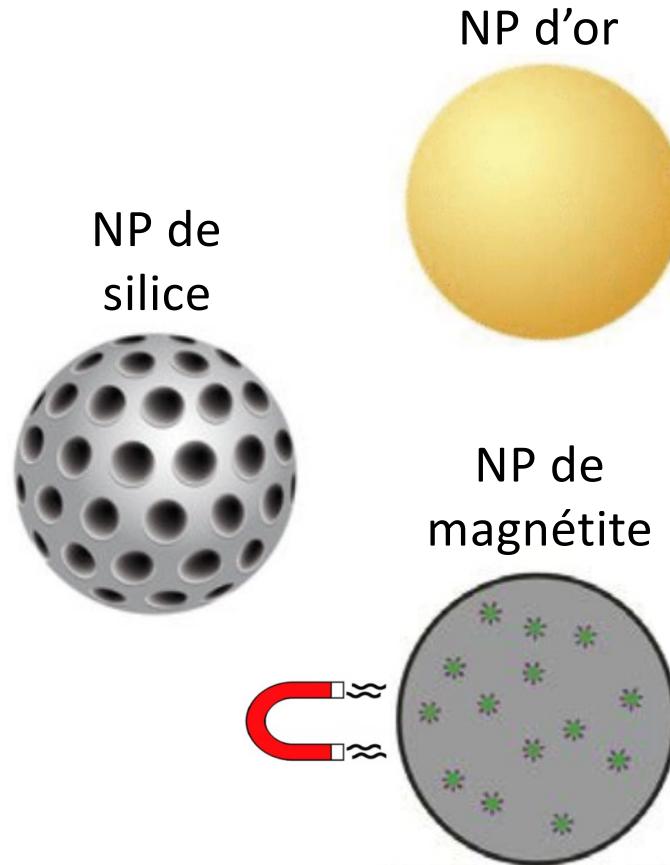


Amélioration biodisponibilité

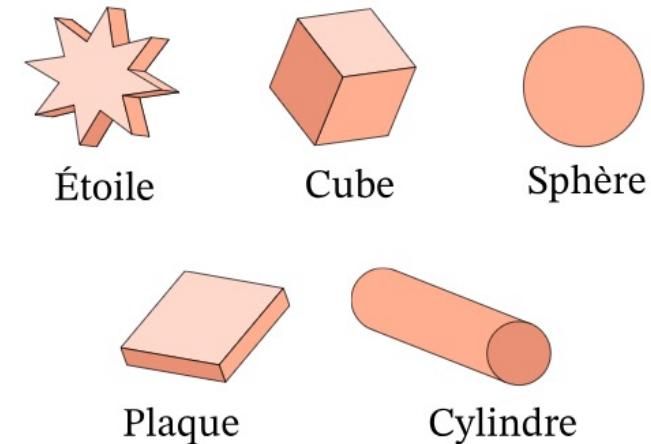
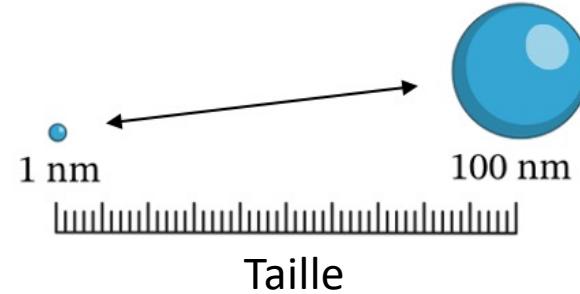
Limitation des effets indésirables



### NP inorganiques

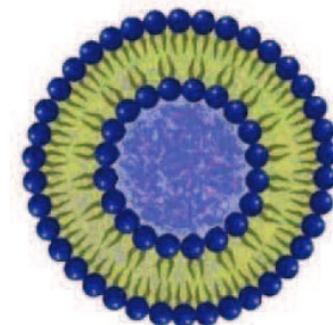


### 3 dimensions



### NP organiques

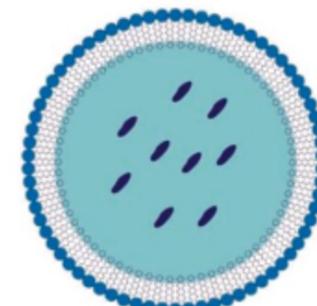
#### Liposomes



#### NP lipidiques solides



#### Nanocapsules lipidiques

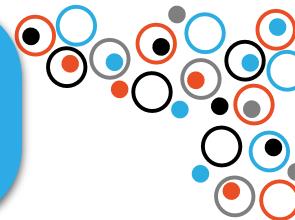


Contexte

Les  
nanoparticules  
dans le CHC

Étude  
préliminaire

Conclusion



NP d'or

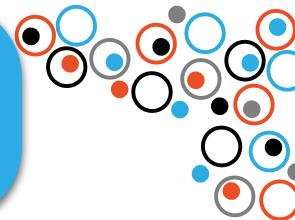


## Contexte

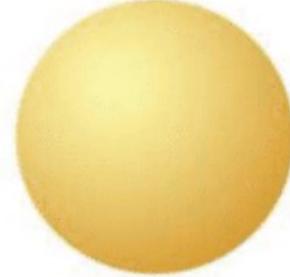
## Les nanoparticules dans le CHC

## Étude préliminaire

## Conclusion



NP d'or



Effet **anti-angiogénique**  
(VEGF-FGF)

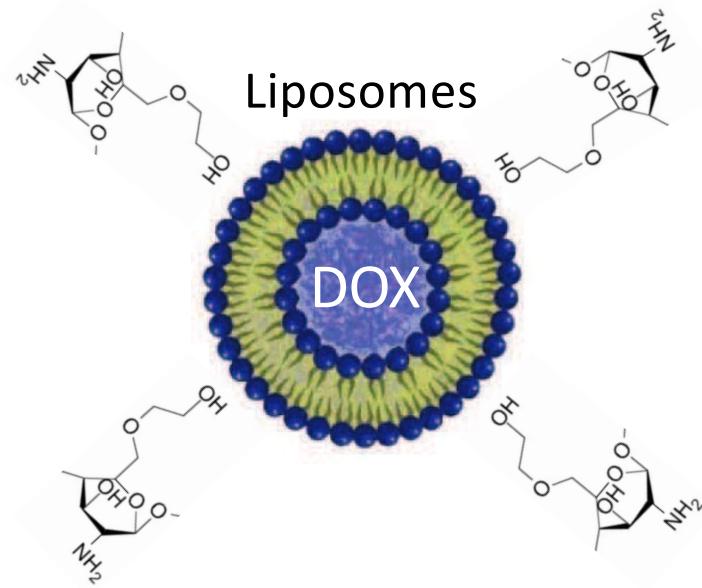
Effet **anti-inflammatoire**  
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## Contexte

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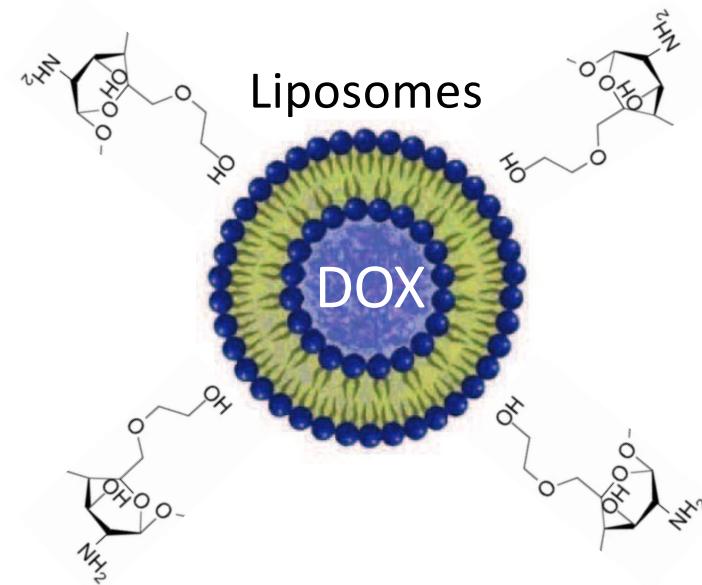
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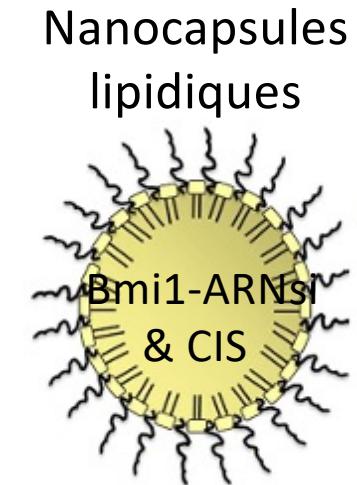
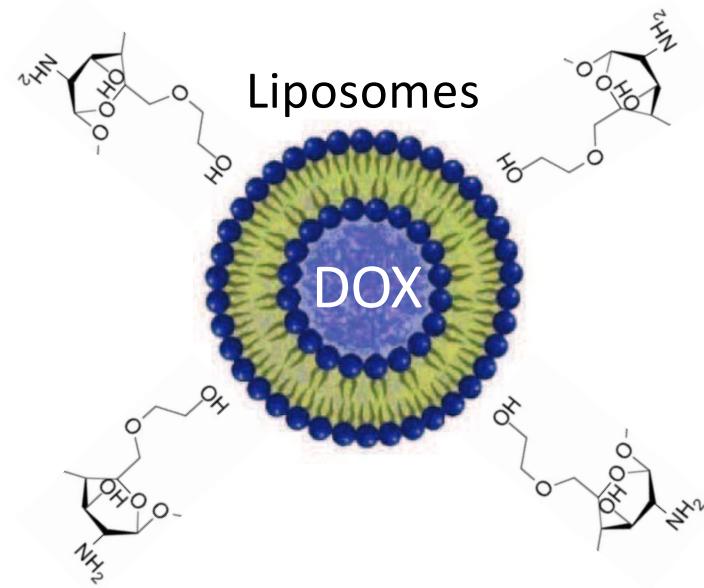
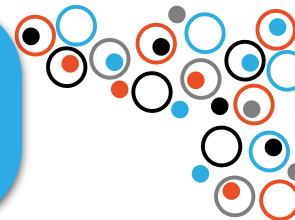
Meilleur ciblage tumoral  
fonctions chitosan  
→ Amélioration **efficacité**  
**thérapeutique**

## Contexte

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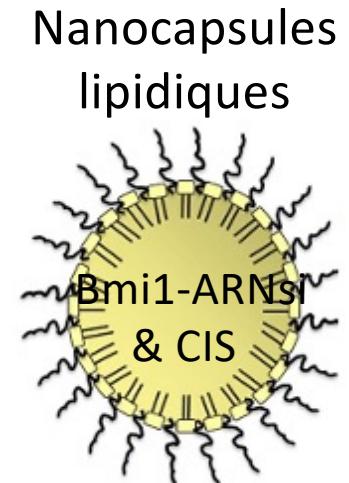
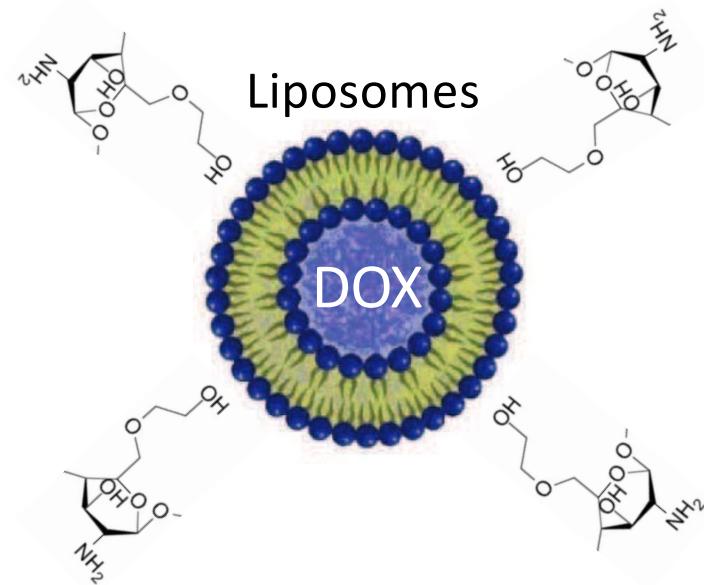
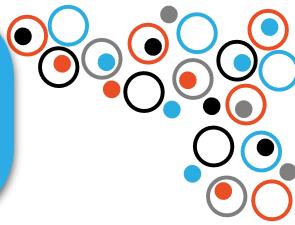
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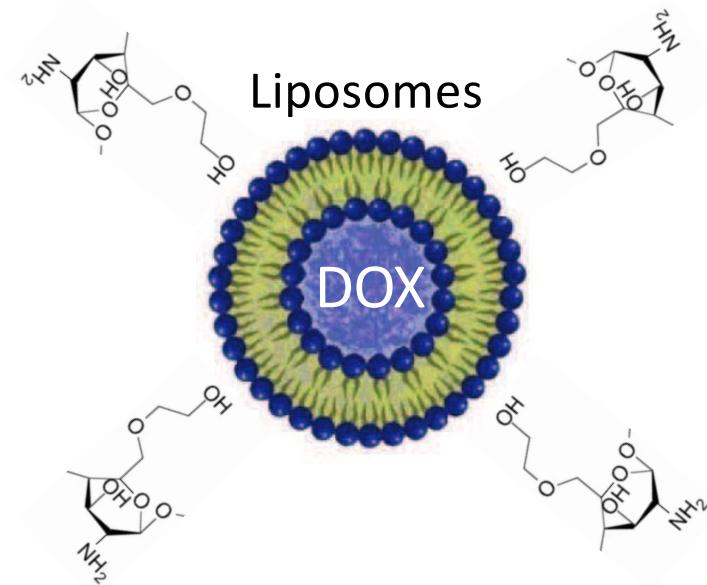
*In vitro* → spécificité  
**ciblage cellules souches**  
*In vivo* → amélioration  
**Activité antitumorale**

## Contexte

NP d'or



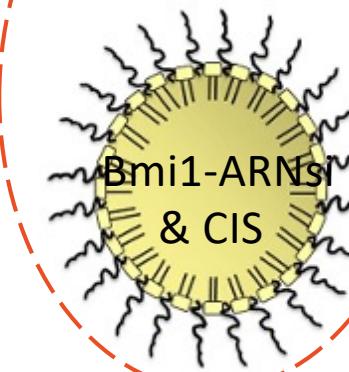
## Les nanoparticules dans le CHC



## Étude préliminaire

## Conclusion

Nanocapsules lipidiques



Effet **anti-angiogénique**  
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Effet **anti-inflammatoire**  
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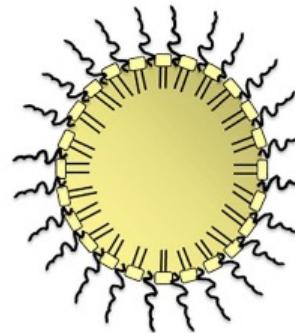
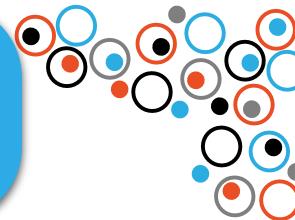
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Contexte

Les  
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Étude  
préliminaire  
Introduction

Conclusion



**NCLs**

Contexte

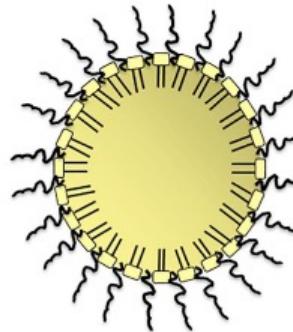
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Amélioration biodisponibilité  
Limitation des effets indésirables



**NCLs**

## Contexte

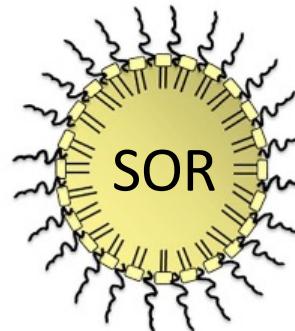
## Les nanoparticules

## Étude préliminaire Introduction

## Conclusion



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**NCLs**

## Contexte

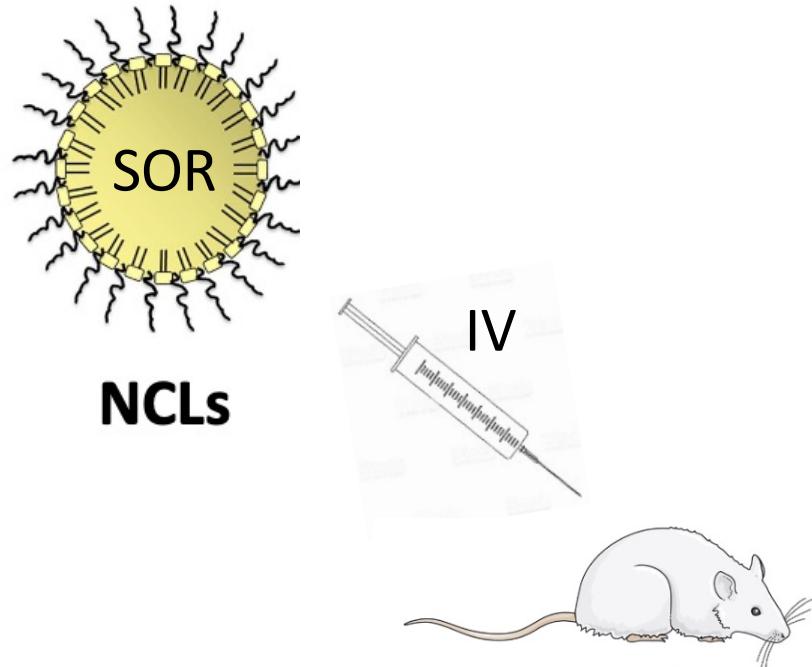
## Les nanoparticules

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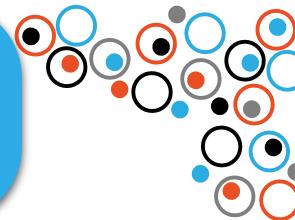


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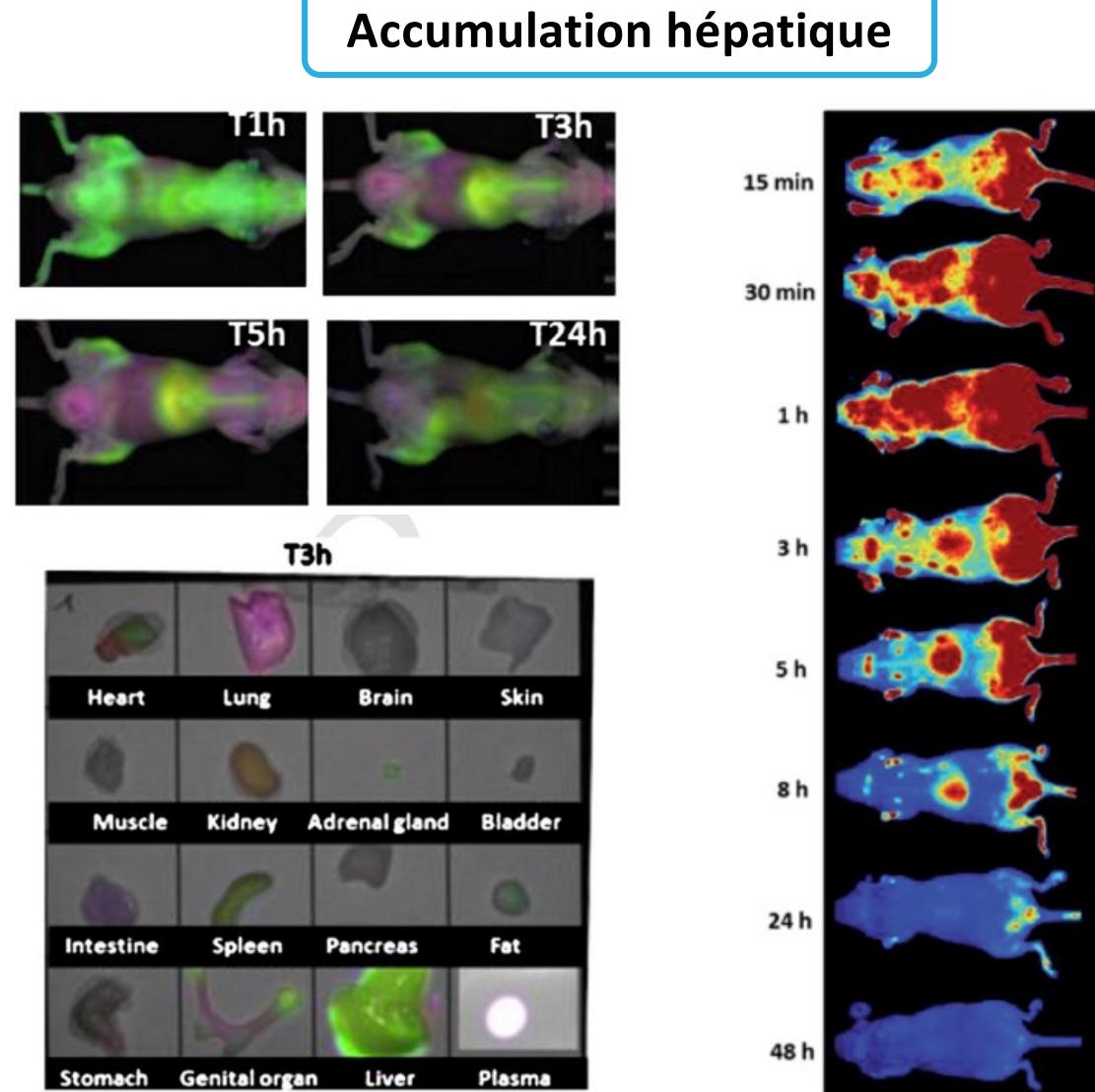
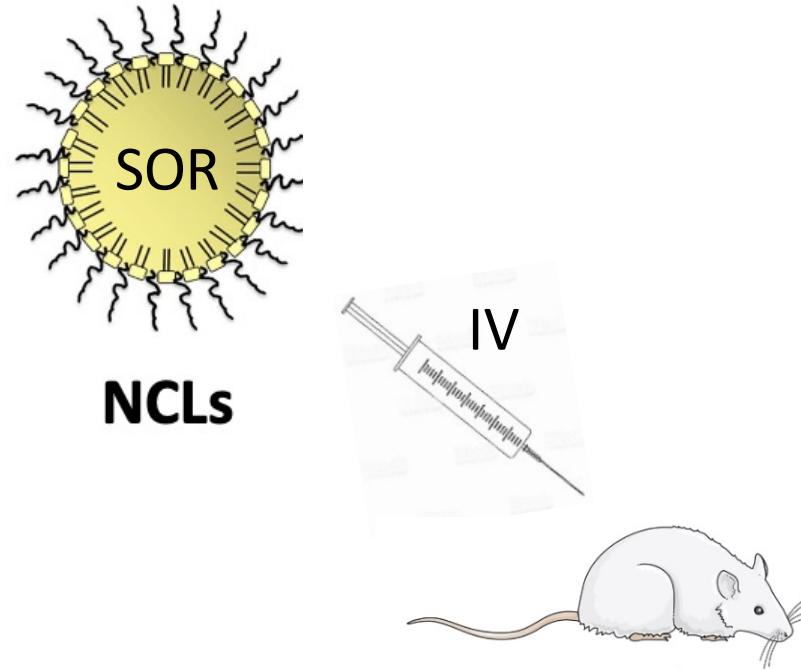
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## Étude préliminaire Introduction

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Amélioration biodisponibilité  
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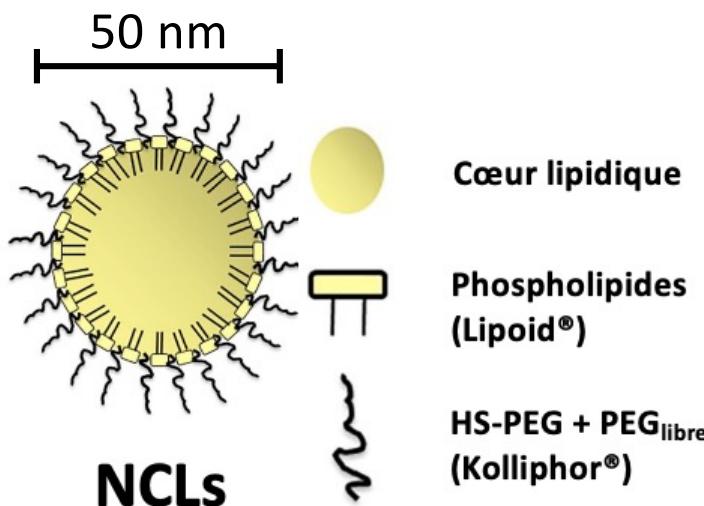


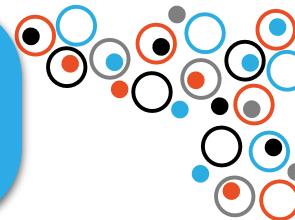
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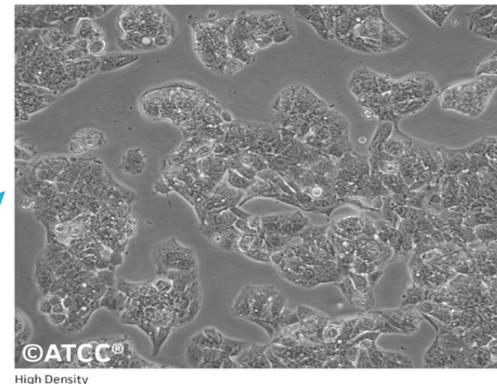
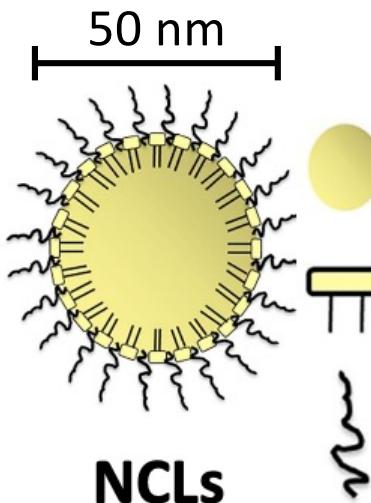
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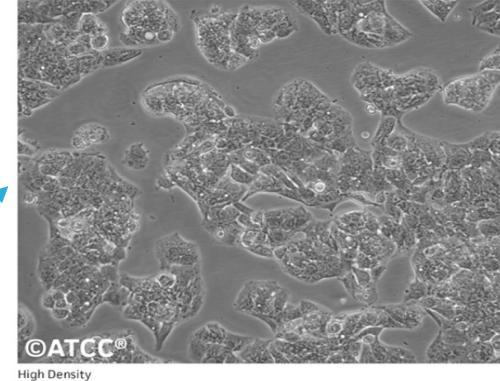
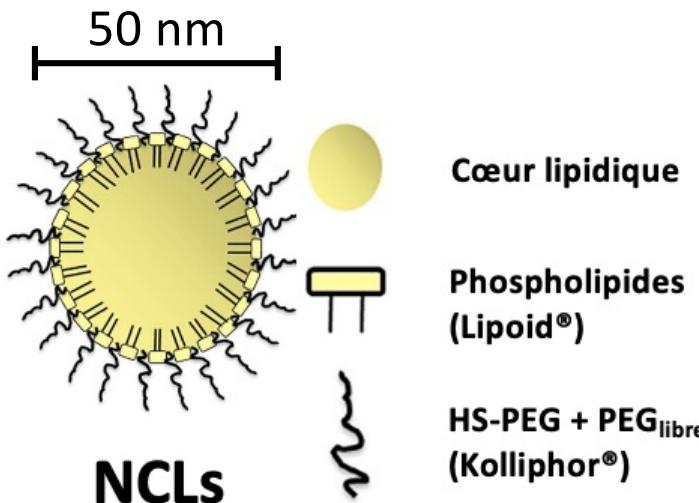
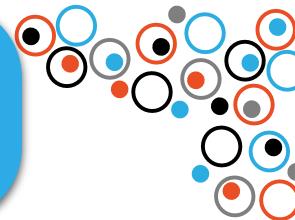
## Conclusion



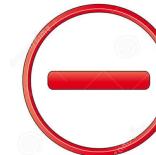


### HepG2





HepG2



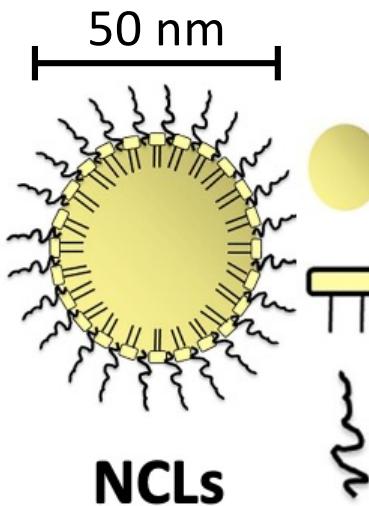
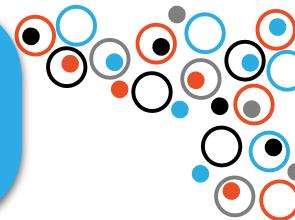
- Faible activité métabolique
- Etudes chroniques impossibles

## Contexte

## Les nanoparticules

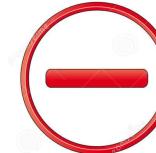
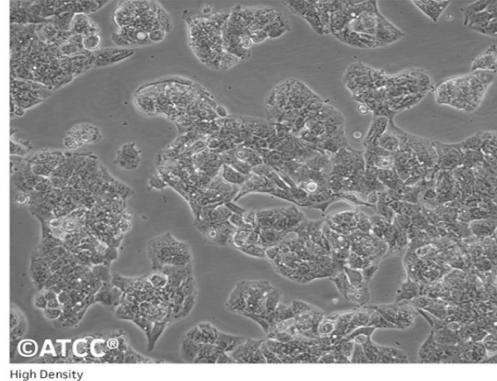
## Étude préliminaire Introduction

## Conclusion



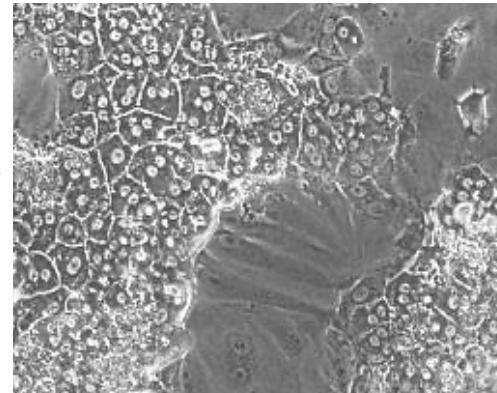
Cœur lipidique  
 Phospholipides (Lipoid®)  
 HS-PEG + PEG<sub>libre</sub> (Kolliphor®)

HepG2



- Faible activité métabolique
- Etudes chroniques impossibles

HepaRG

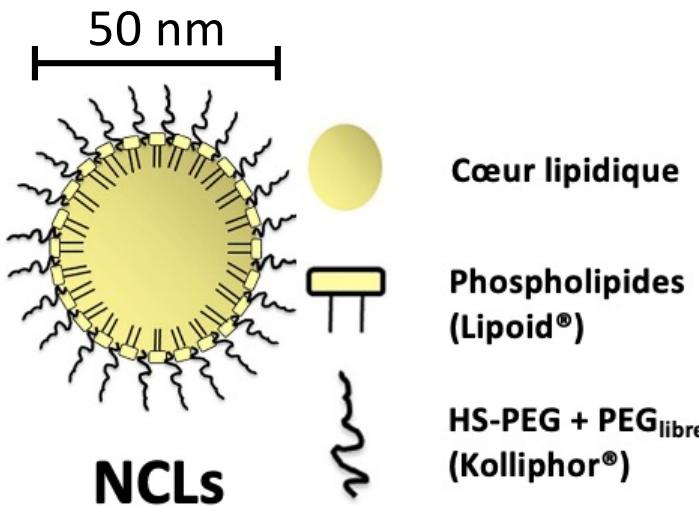
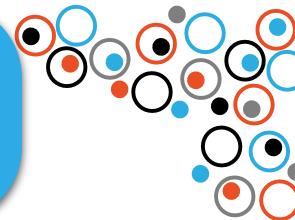


## Contexte

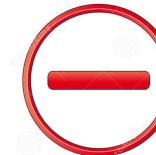
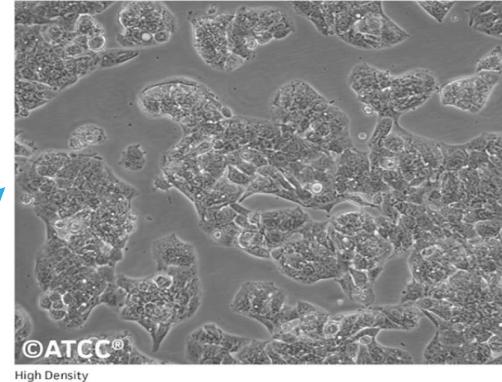
## Les nanoparticules

## Étude préliminaire Introduction

## Conclusion

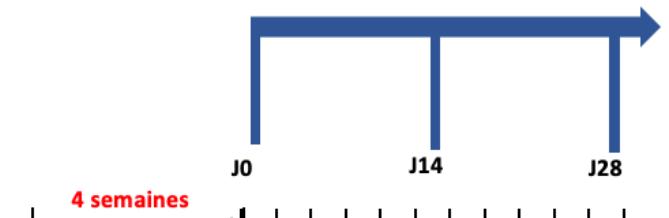
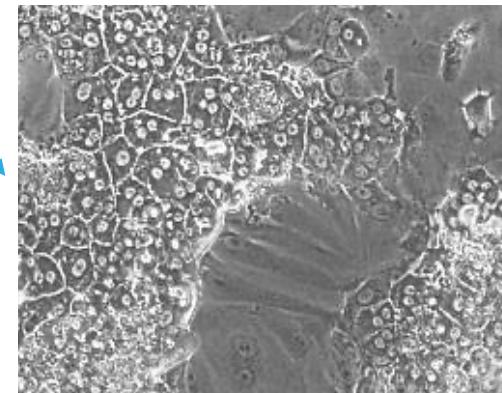


HepG2



- Faible activité métabolique
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HepaRG

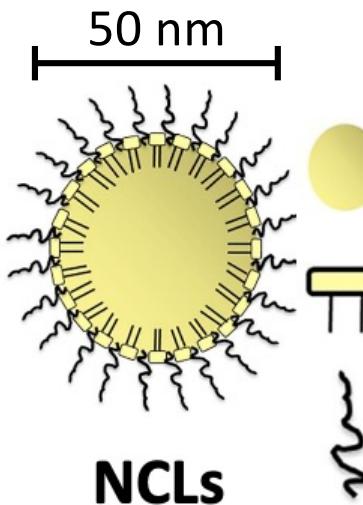
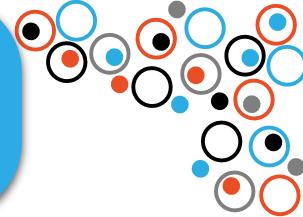


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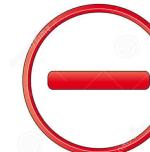
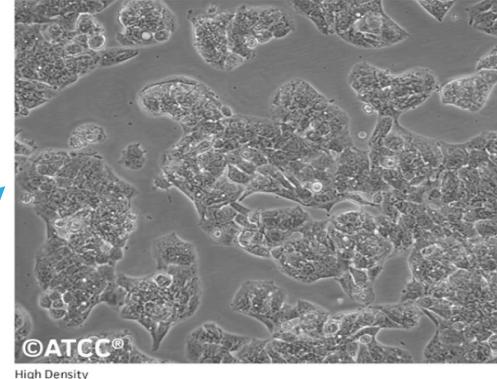
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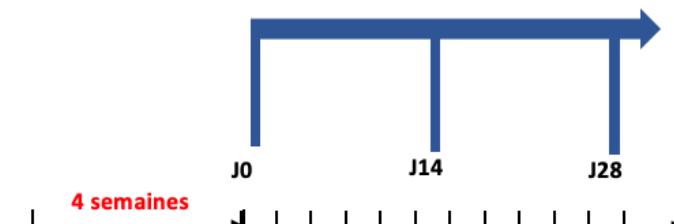
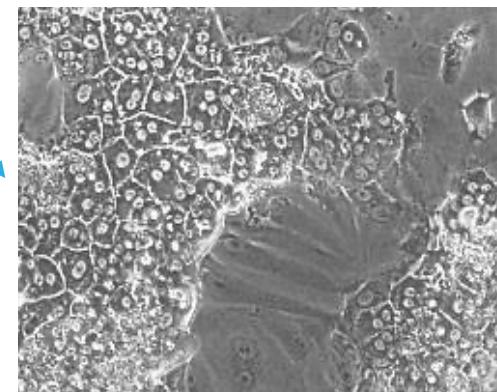


HepG2



- Faible activité métabolique
- Etudes chroniques impossibles

HepaRG



- Modèle proche des hépatocytes humains en culture primaire
- Stable pendant un mois

## Contexte

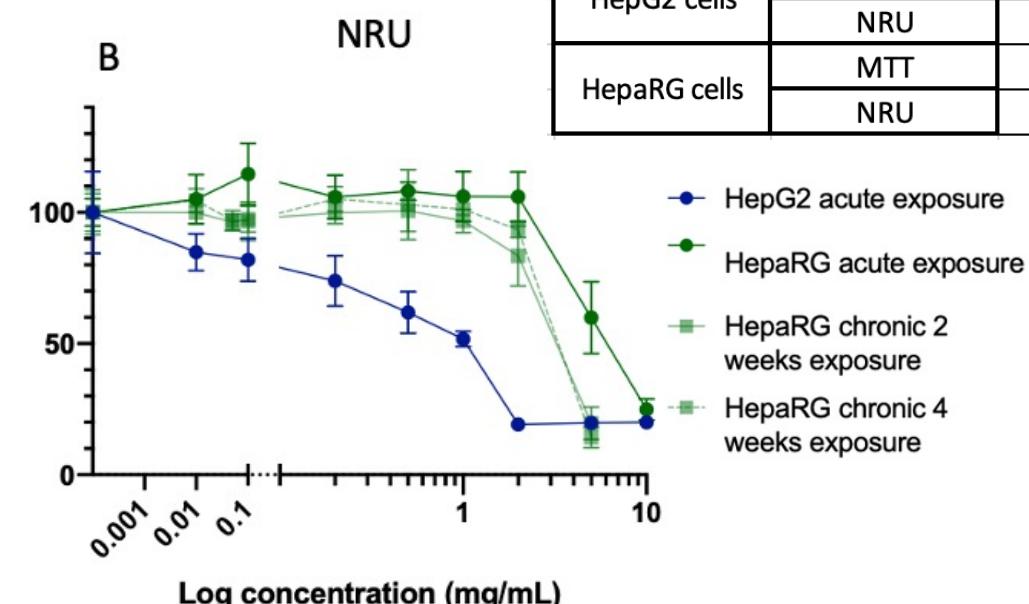
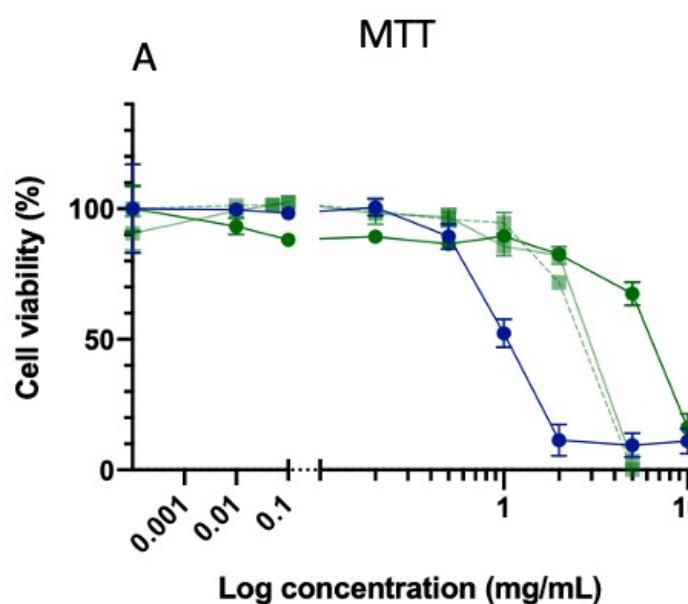
## Les nanoparticules

## Étude préliminaire Toxicité/innocuité

## Conclusion

→ Évaluation de la toxicité/biocompatibilité

CL50



Cell line	Type of assay	Time of exposure (days)		
		1	14	28
HepG2 cells	MTT	$0.91 \pm 0.02 *$		
	NRU	$0.77 \pm 0.21 *$		
HepaRG cells	MTT	$6.37 \pm 0.82 *$	$3.30 \pm 0.16 +$	$2.40 \pm 0.28 +$
	NRU	$6.91 \pm 1.25 *$	$3.25 \pm 0.91 +$	$3.68 \pm 0.70 \#$

Mann Whitney test. \*, + and # ( $p < 0.05$ ) represent a significative difference between cell lines, time of exposure and type of assay, respectively

## Contexte

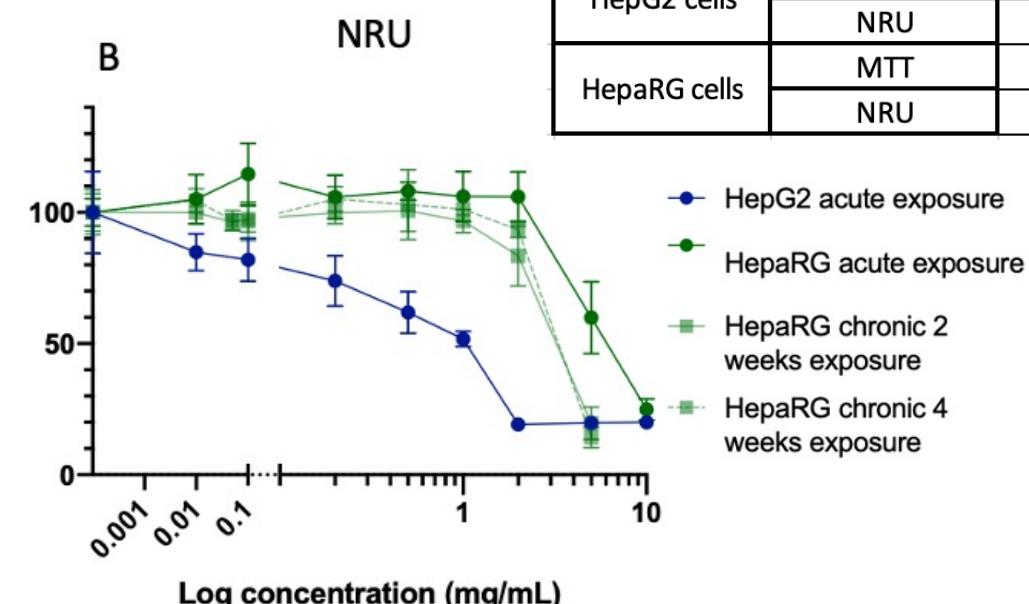
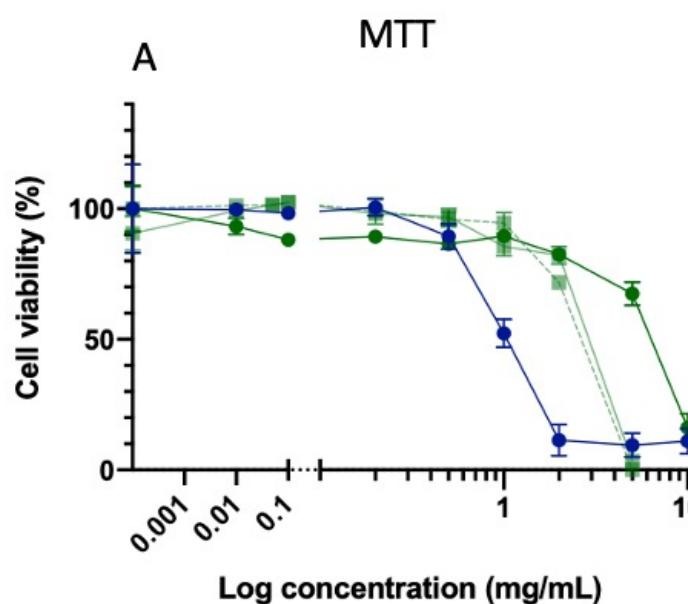
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Toxicité plus importante sur la lignée cancéreuse : cellules **HepG2 plus sensible aux NCLs que HepaRG**

## Contexte

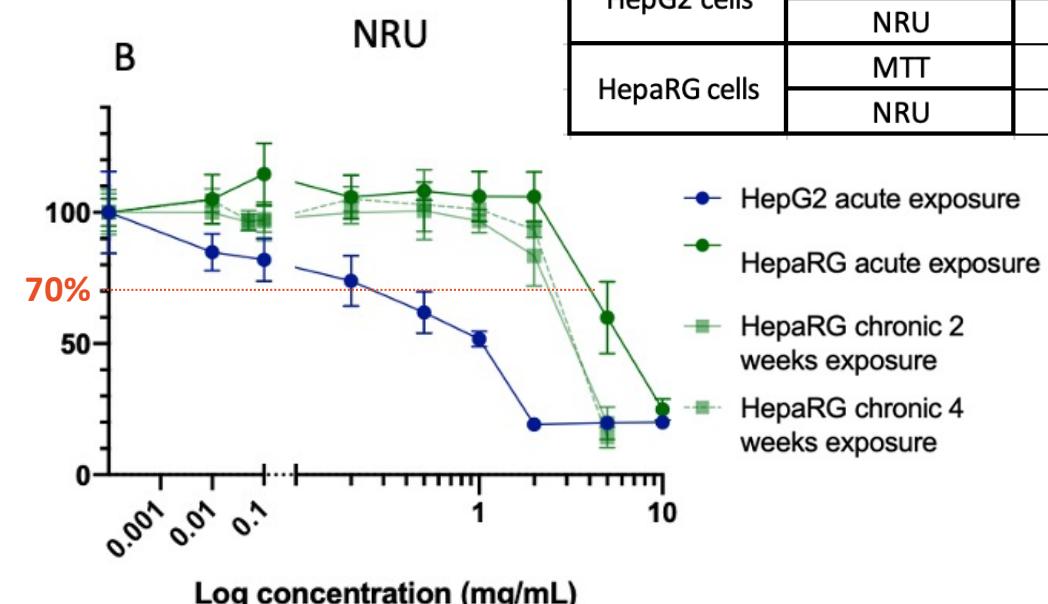
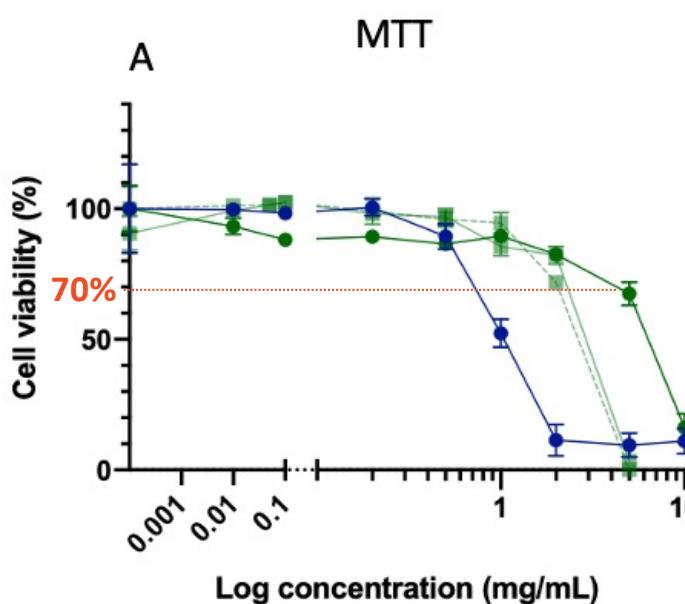
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**Biocompatibilité des NCLs sur les cellules HepaRG à de fortes doses, jusqu'à 28 jours d'exposition**

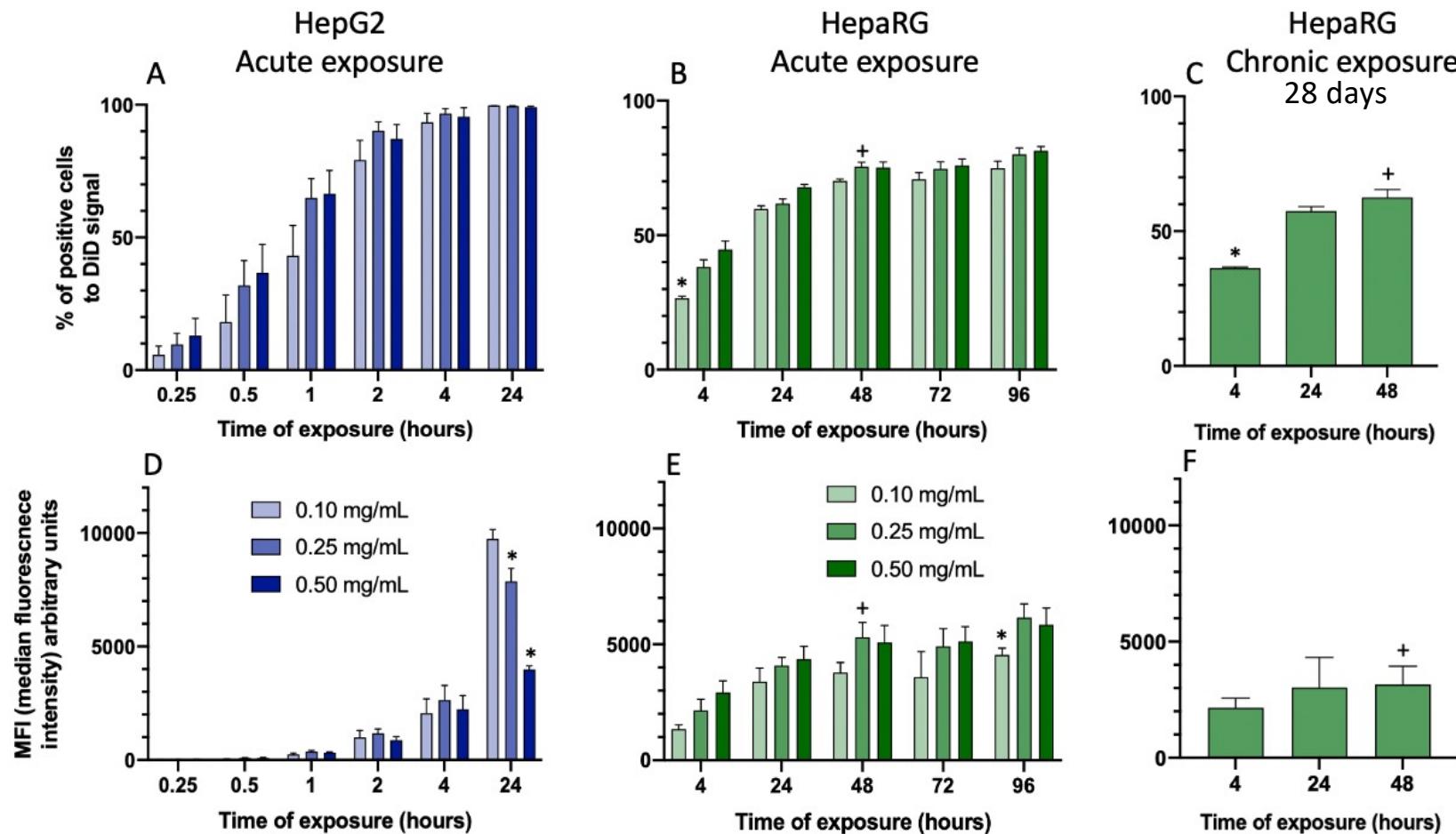
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## Les nanoparticules

## Étude préliminaire Ciblage ?

## Conclusion

### → Évaluation des cinétiques d'internalisation



Mann Whitney test. \* and + ( $p < 0.05$ ) represent a significant difference between concentration and time of exposure, respectively

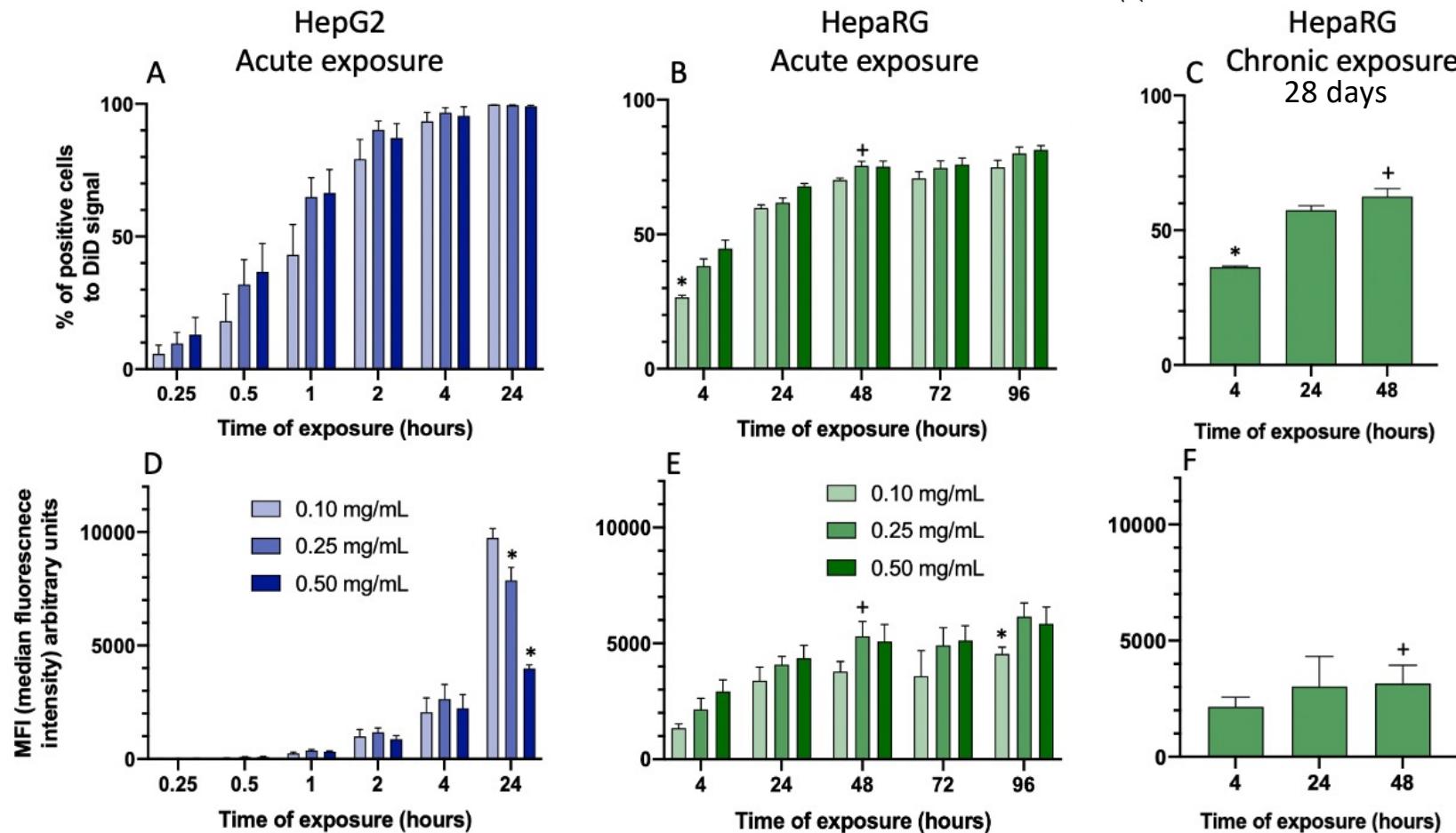
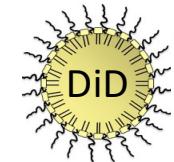
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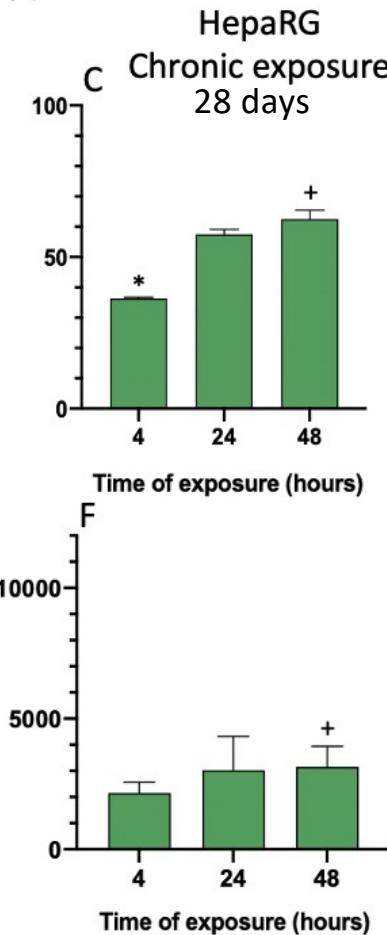
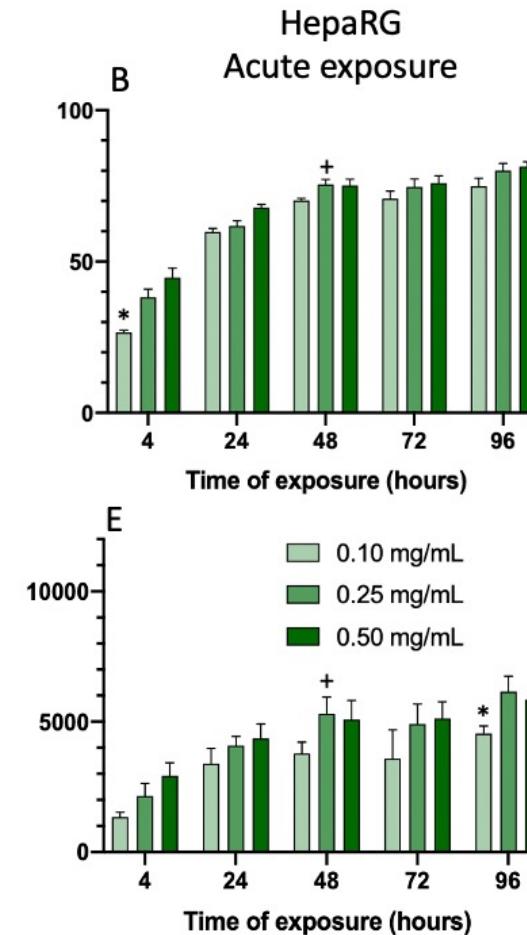
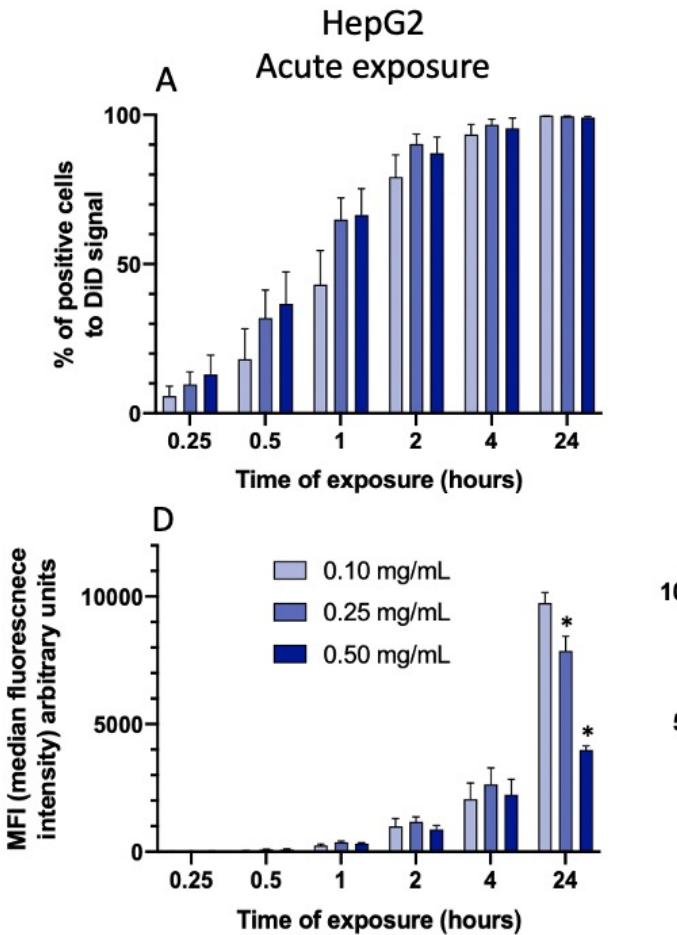
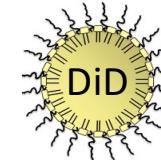
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**HepG2**  
Internalisation **rapide**  
**& complète**  
Forte accumulation  
intracellulaire

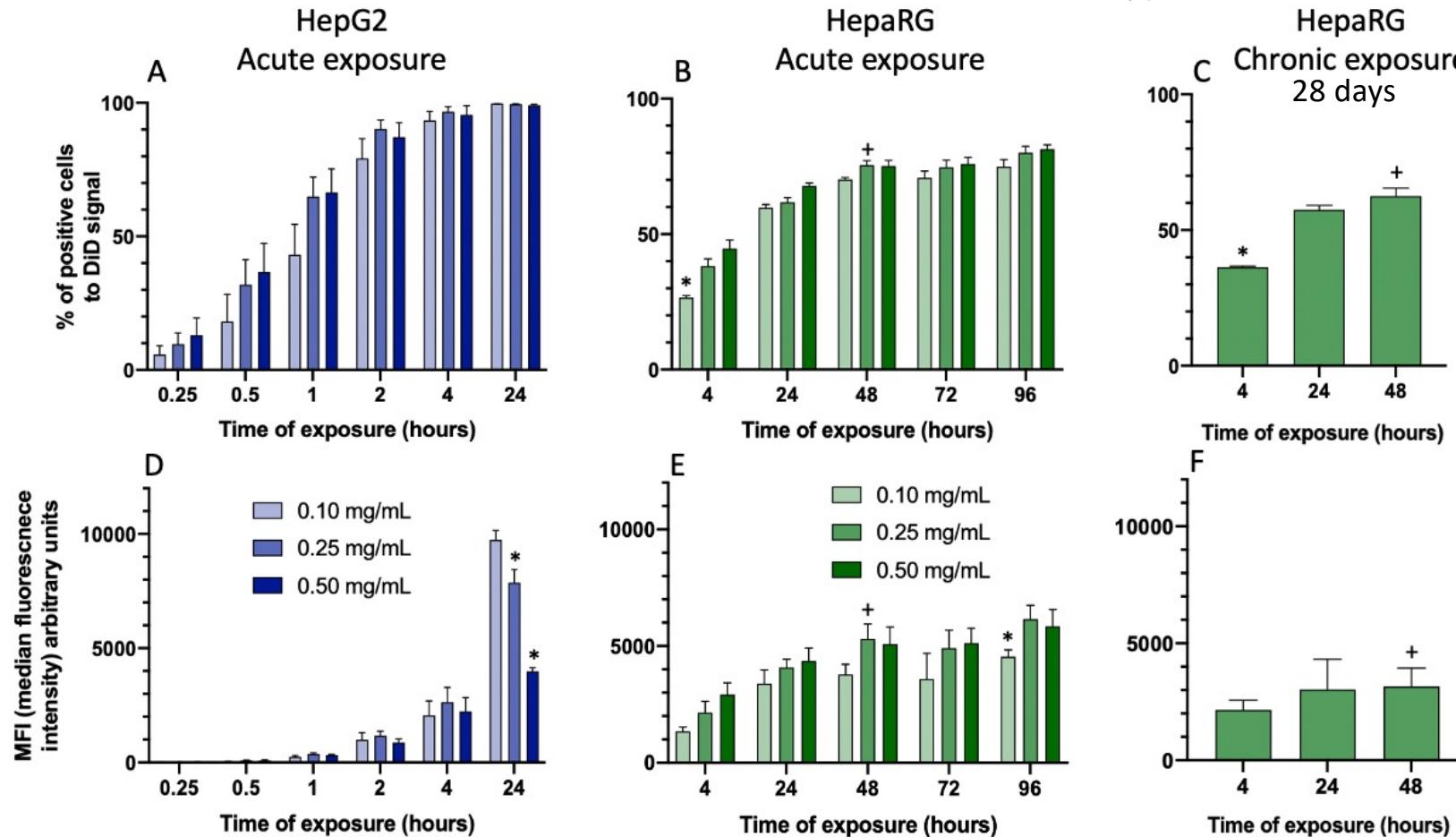
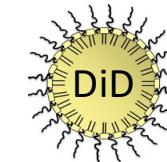
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VS.

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Accumulation  
Intracellulaire saturable

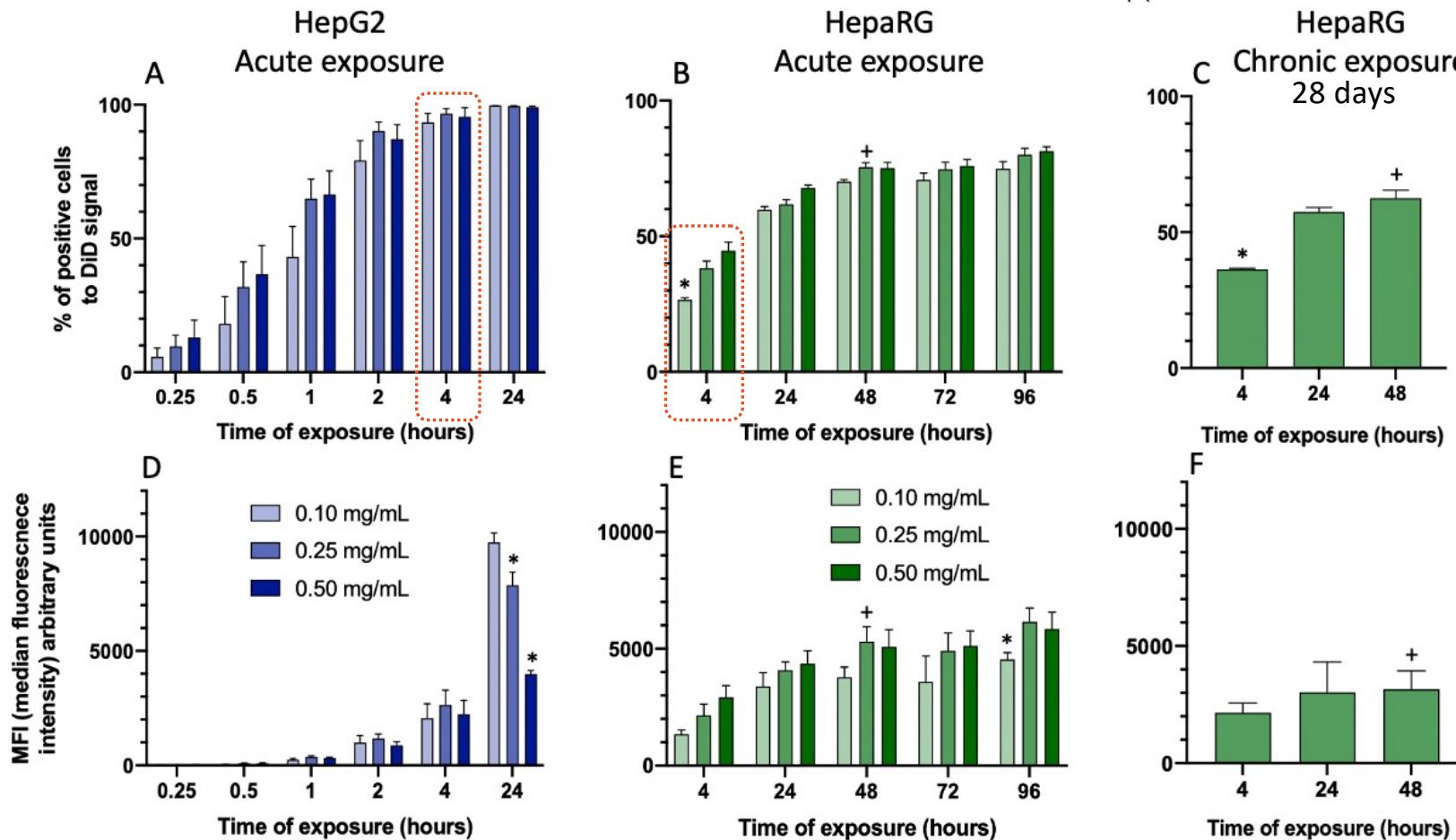
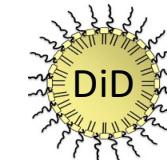
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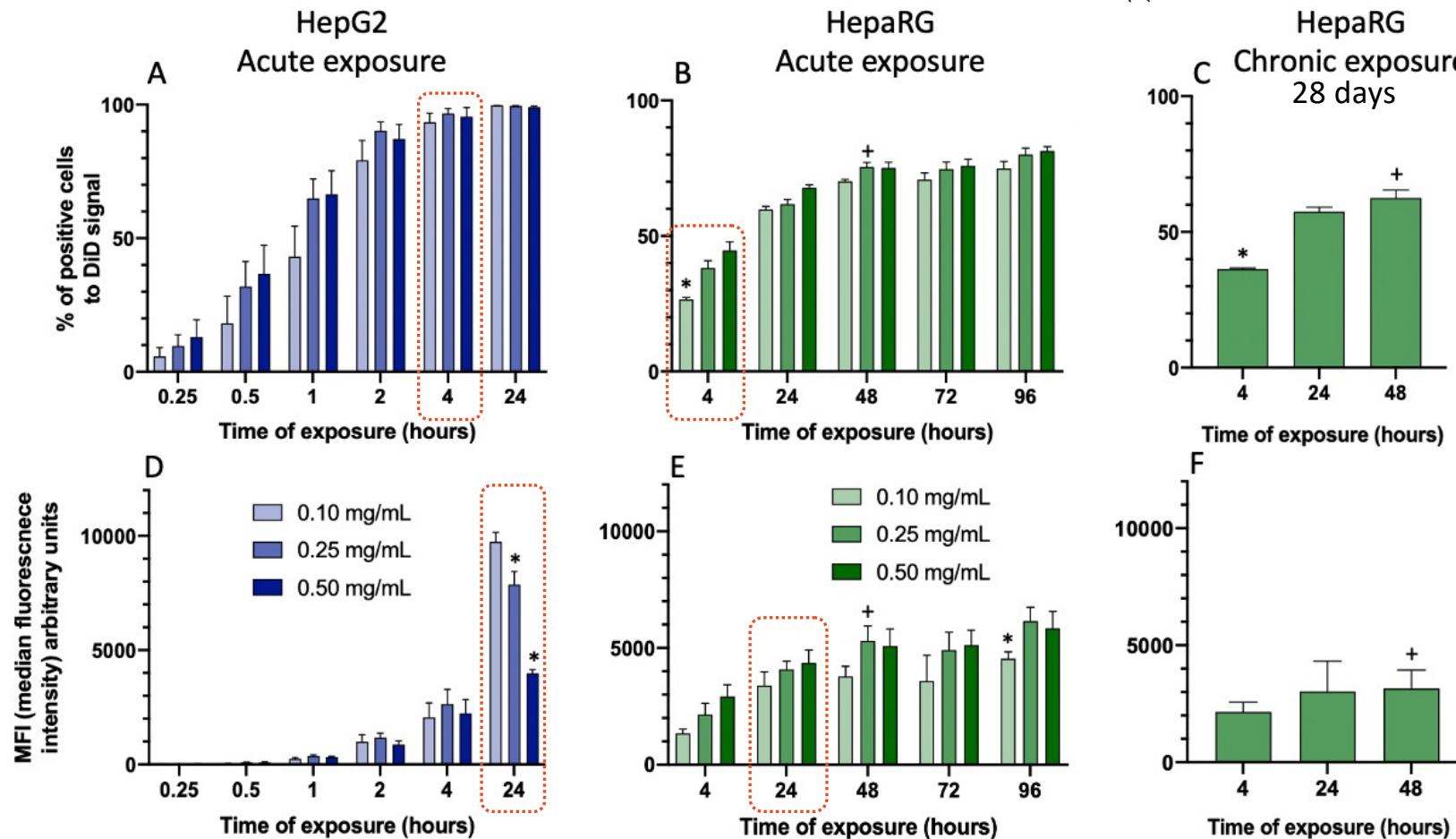
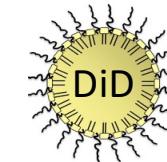
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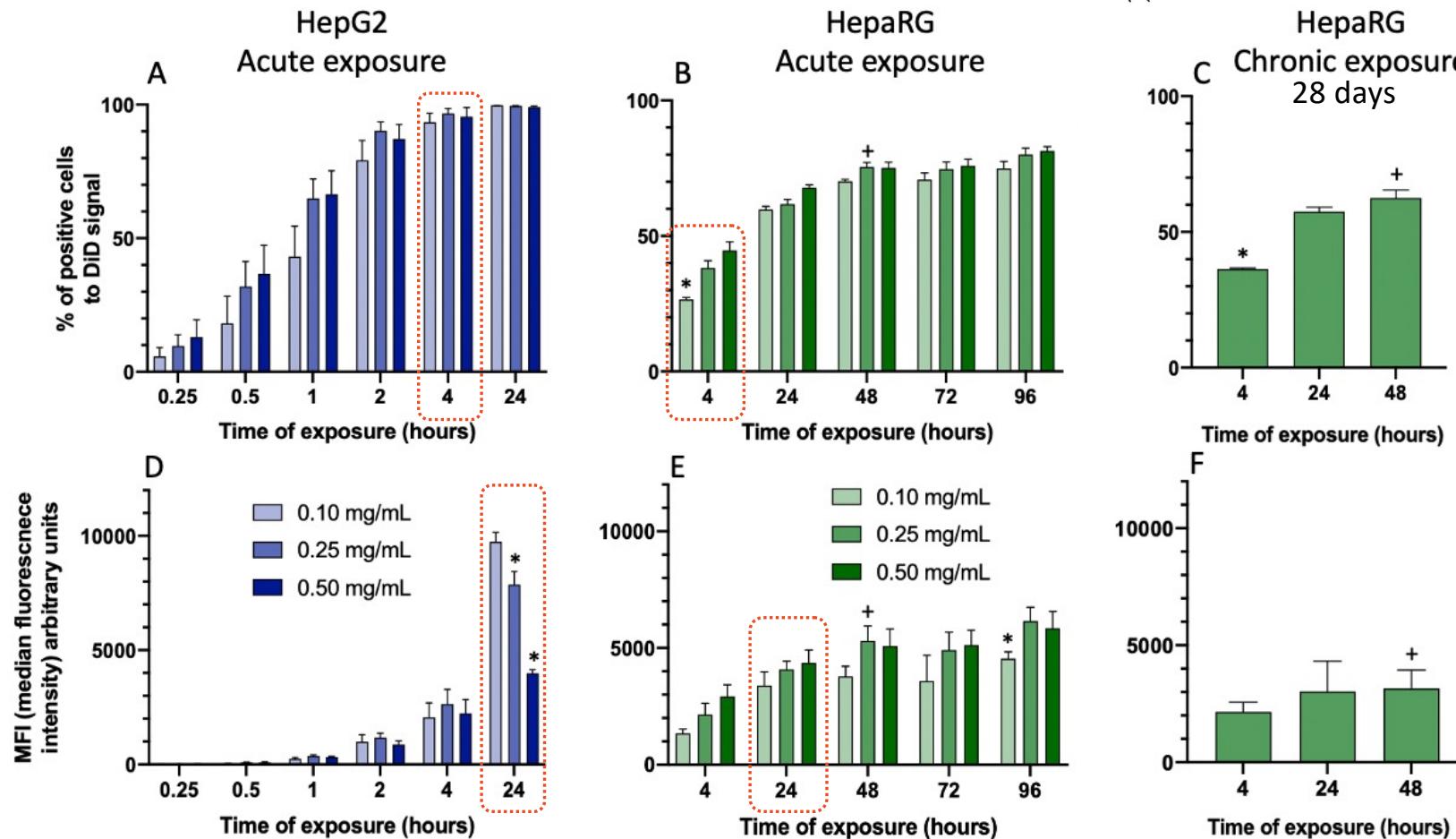
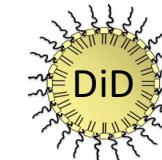
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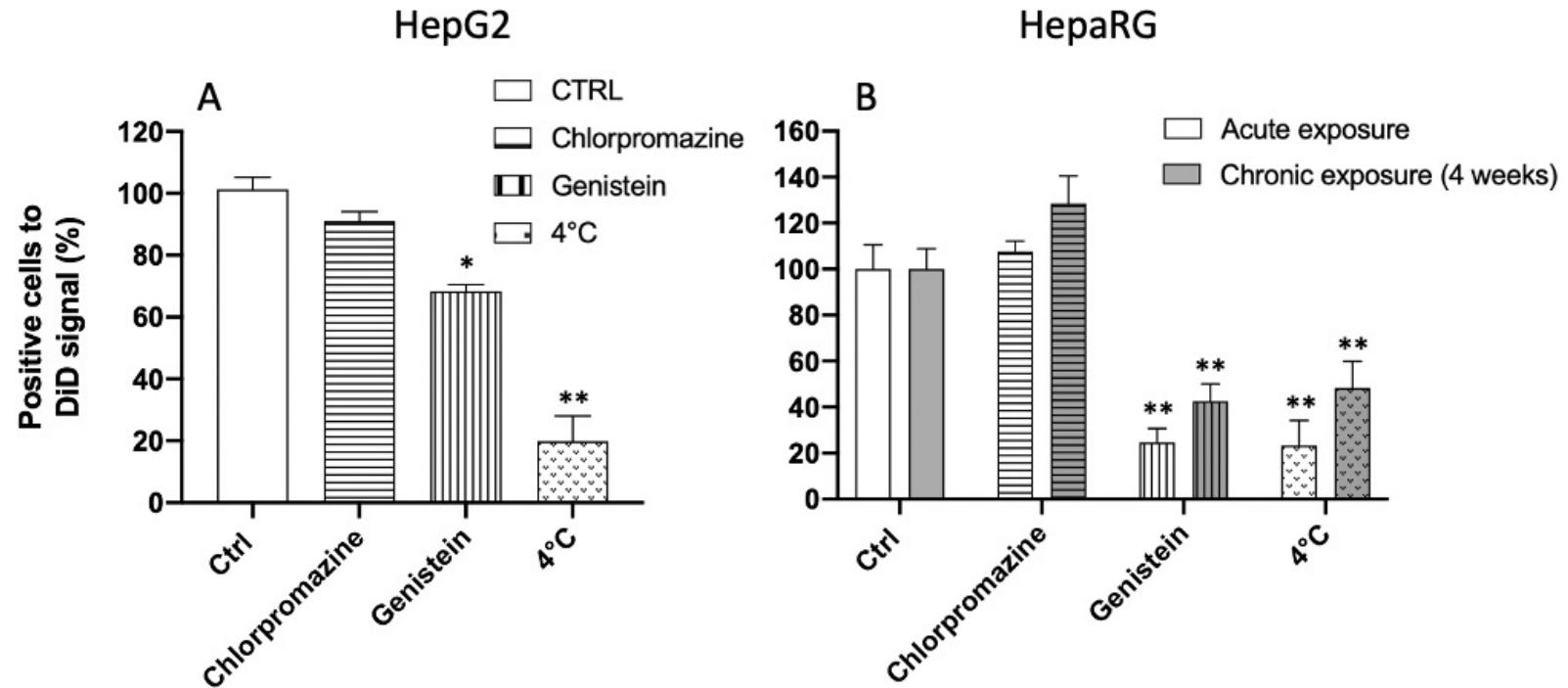
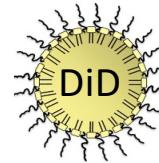
## Contexte

## Les nanoparticules

## Étude préliminaire Pathways

## Conclusion

### → Exploration des voies d'internalisation



Chlorpromazine = inhibiteur de l'endocytose clathrine-dépendante

Génistéine = inhibiteur de l'endocytose cavéoline-dépendante

4°C = diminue fortement le métabolisme & rigidifie les membranes

Test de Kruskal-Wallis. \* ( $p < 0.05$ ) and \*\* ( $p < 0.01$ ) represent a significative difference compared to control

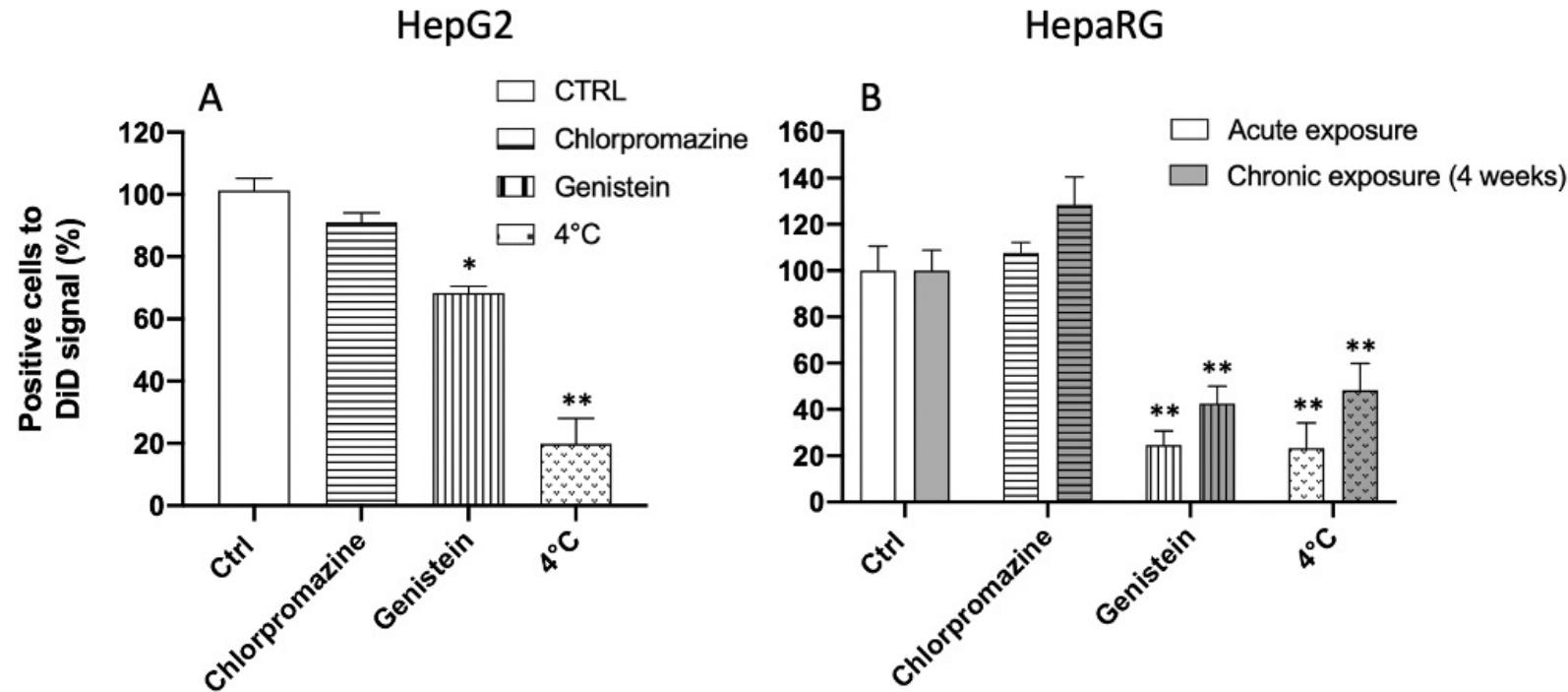
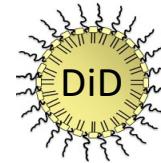
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**Internalisation active via endocytose cavéoline-dépendante**

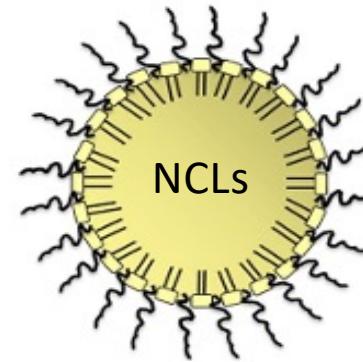
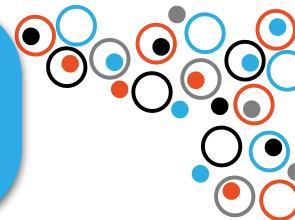
**Temps d'exposition n'influence pas les voies d'internalisation**

## Contexte

## Les nanoparticules

## Étude préliminaire

## Conclusion



Intérêt dans le traitement du CHC ?

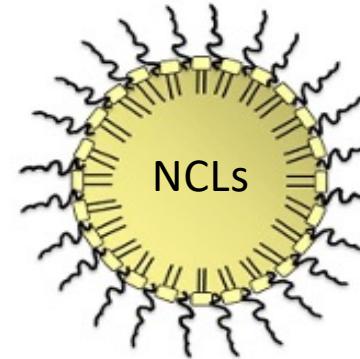
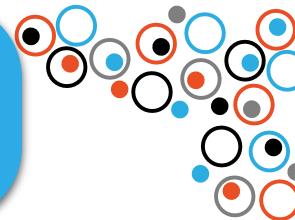


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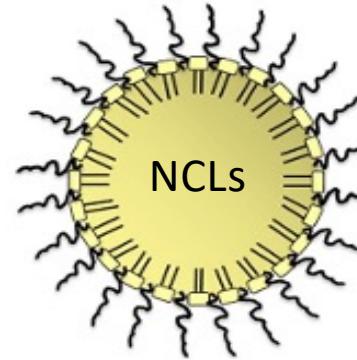
Taux d'encapsulation élevés de divers anticancéreux (SOR, CIS, DOX)  
&  
**diminution des effets indésirables + augmentation de la biodisponibilité**

## Contexte

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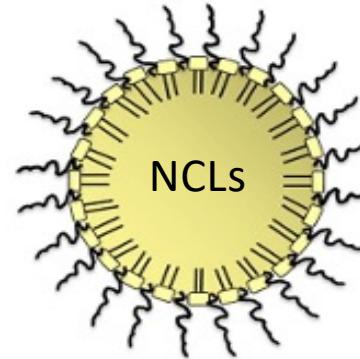
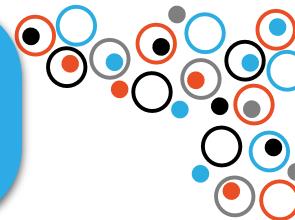
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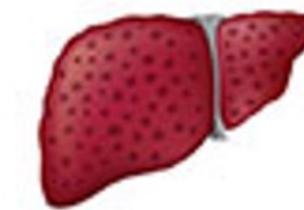
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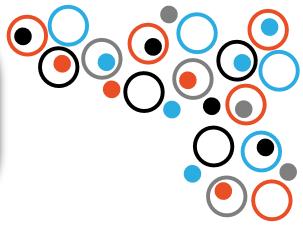
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Bonne **biocompatibilité** *in vitro* après **exposition aiguë et chronique**



Merci pour votre attention



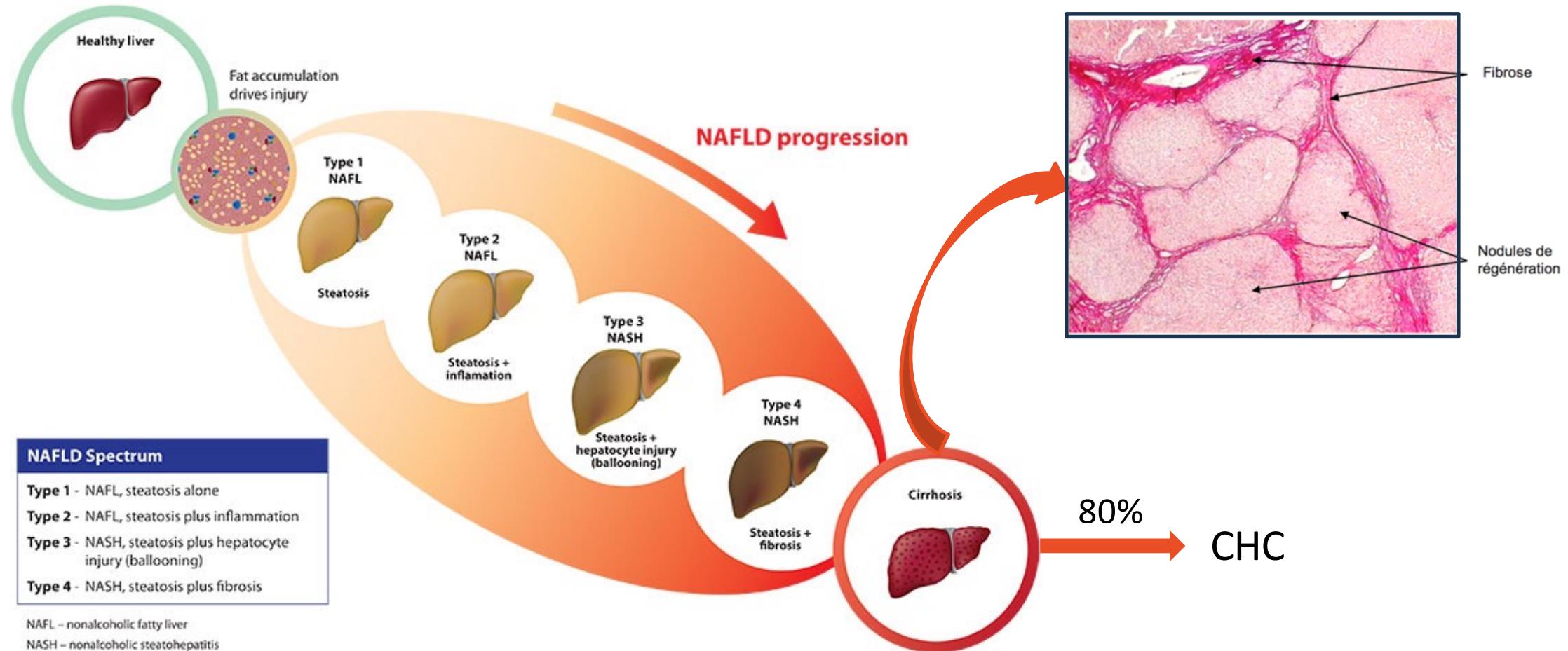
Q & A

## Contexte Évolution du CHC

## Les nanoparticules

## Résultats préliminaires

## Conclusion

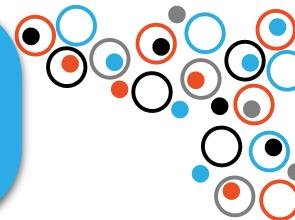


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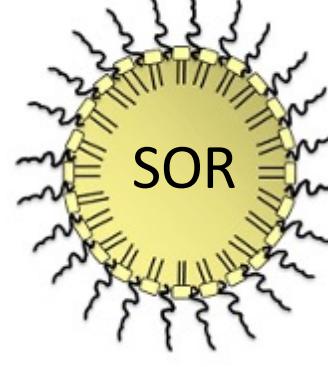
## Les nanoparticules

## Résultats préliminaires

## Perspectives



NCLs



IV

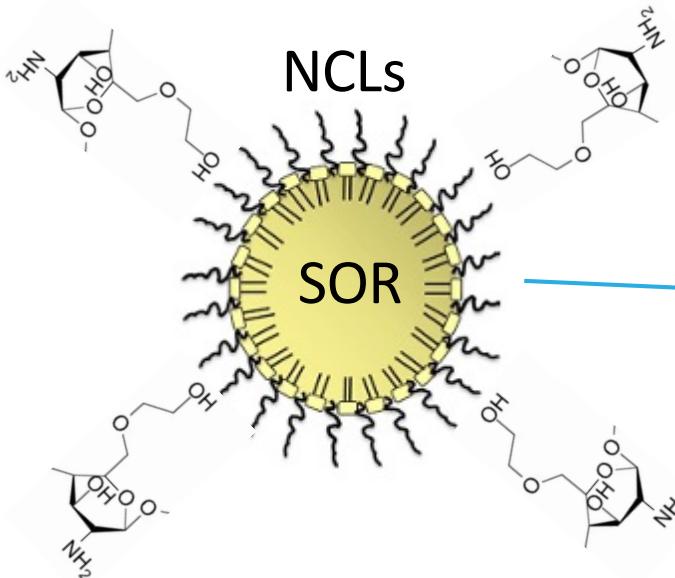


Ciblage tumoral

Régression tumeur

Tolérance/survie

Rat mâle  
Wistar porteur  
CHC



IV



Efficacité thérapeutique  
Biocompatibilité