



In vitro evaluation of acute and chronic liver toxicity of lipid nanocapsules

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Flavien Delaporte, Emilie Roger, Frédéric Lagarce, Camille Savary. In vitro evaluation of acute and chronic liver toxicity of lipid nanocapsules. Journée de la Société Française de Recherche ICAT, Jun 2022, Angers, France. <hal-03695378>

HAL Id: hal-03695378

<https://hal.science/hal-03695378v1>

Submitted on 14 Jun 2022

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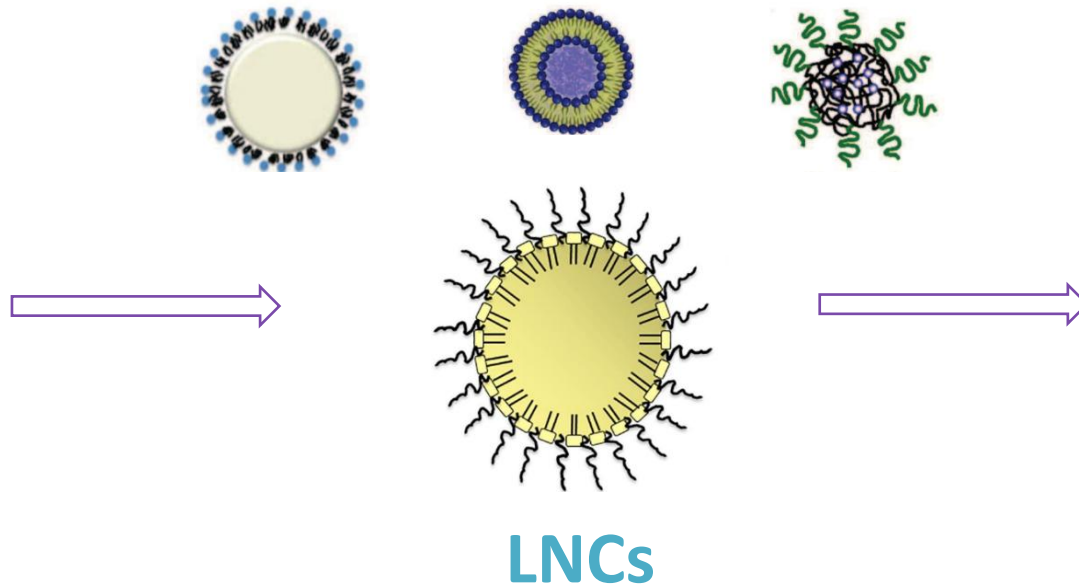
In vitro evaluation of acute and chronic liver toxicity of lipid nanocapsules (LNCs)

Flavien Delaporte

Emilie Roger, Frédéric Lagarce, Camille Savary

MINT (Micro et Nanomédecines Translationelles) UMR 1066 CNRS 6021

Context



Better kinetics
Decrease side effects
Fonctionalization/targeting

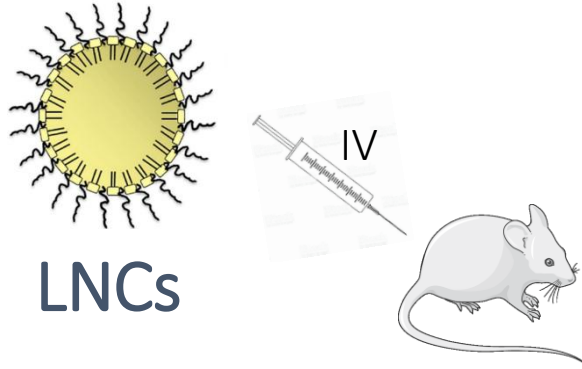
Cancers

**Chronic
therapy**

Context

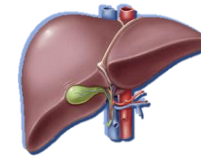


Ovarian
Breast
Glioblastoma
Melanoma

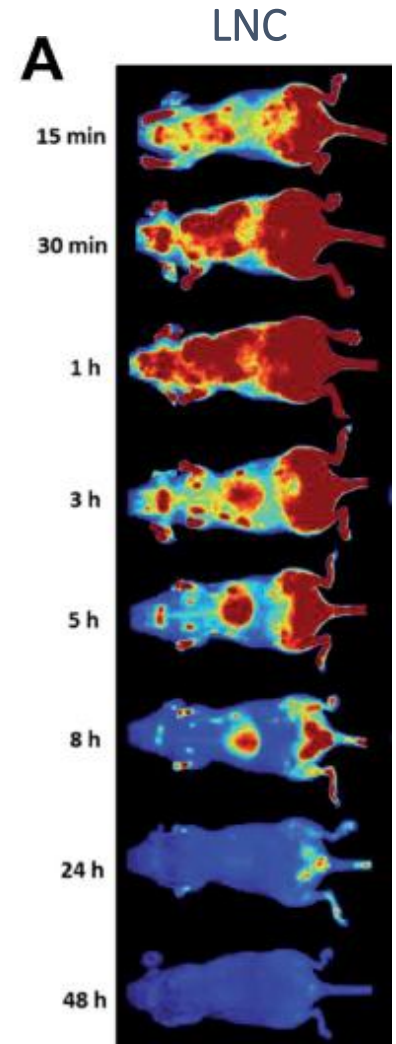


LNCs as treatment
for hepatic cancer?

Hepatic tropism



Need for hepatic
toxicity studies



Objective



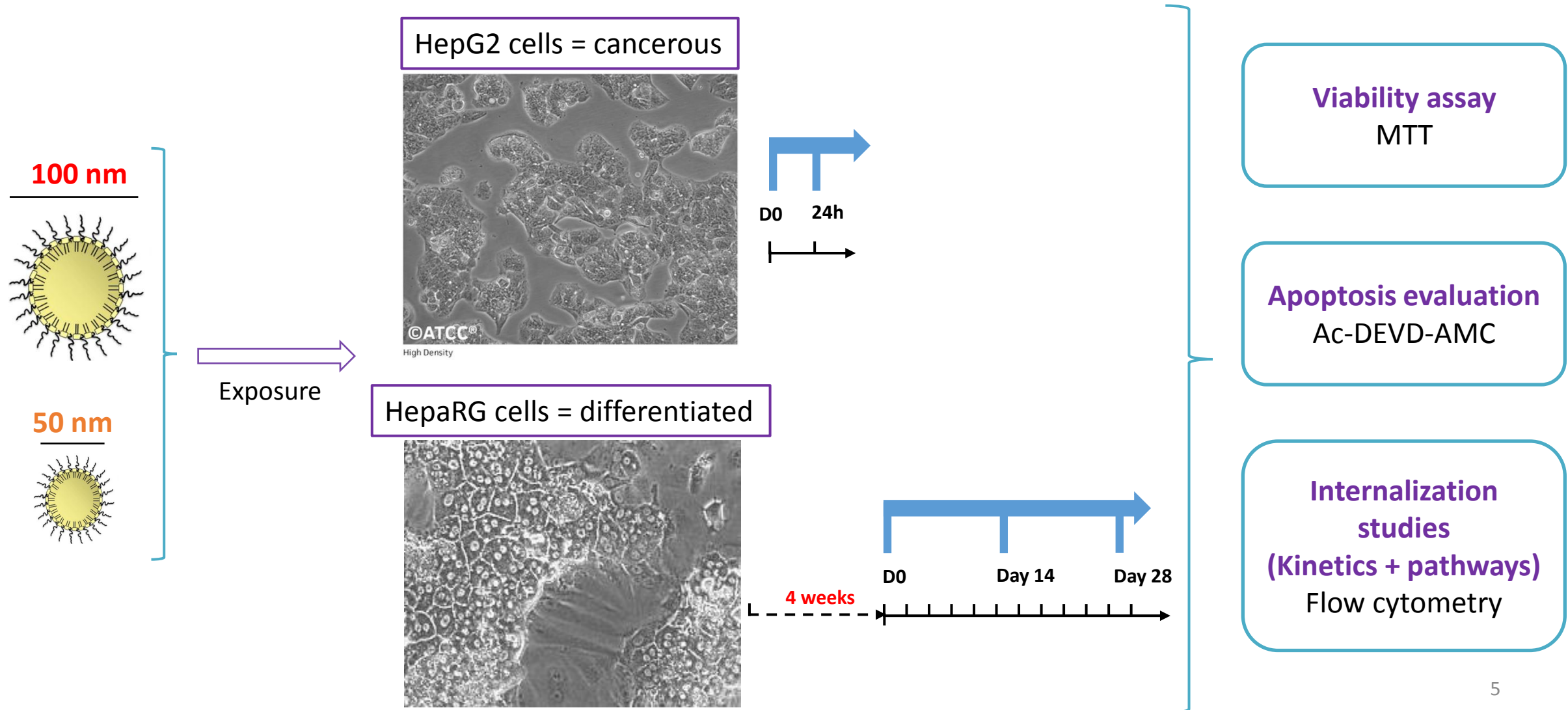
Few studies on
hepatotoxicity



In vitro evaluation of acute and chronic liver toxicity of
LNCs

1. Is there a **size effect** on LNCs's toxicity?
2. Are there **chronic effects** after repeated exposure?

Methods



Objective



Few studies on
hepatotoxicity



In vitro evaluation of acute and chronic liver toxicity of
LNCs

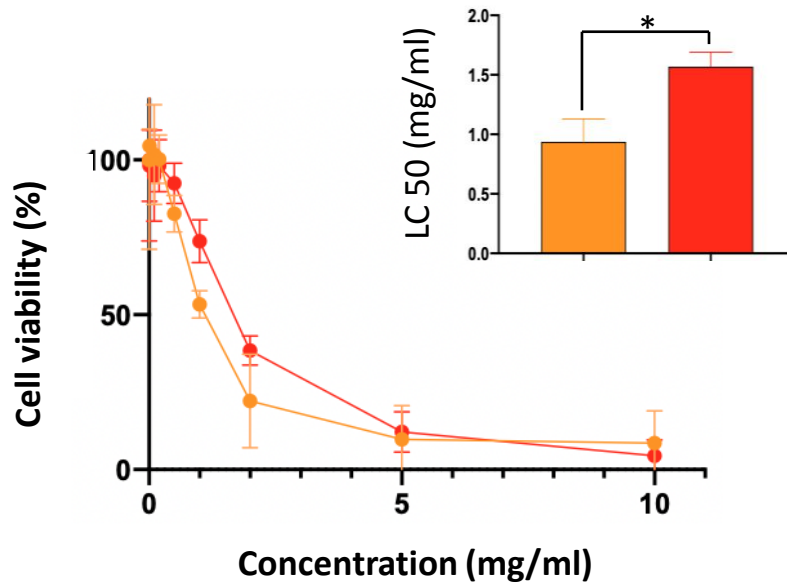
1. Is there a **size effect** on LNCs's toxicity?
2. Are there chronic effects after repeated exposure?

Results: is there a size effect?



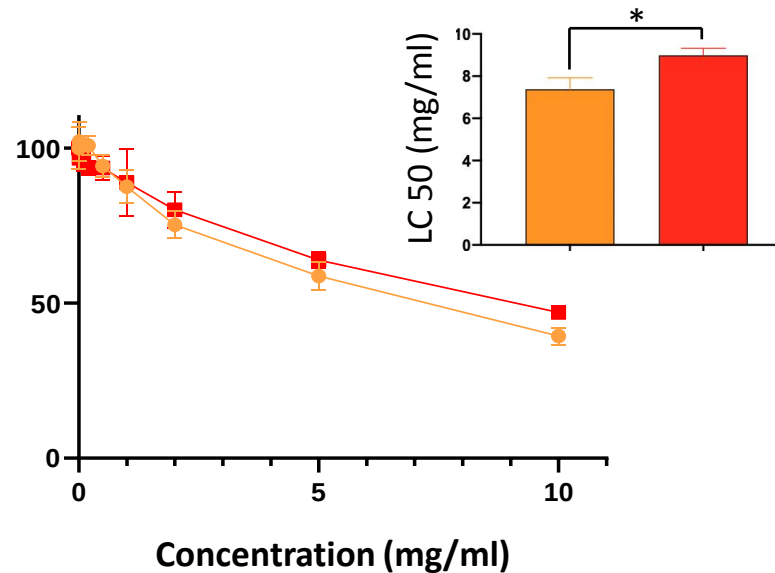
Viability on **HepG2 cells** (n = 4)

24h treatment

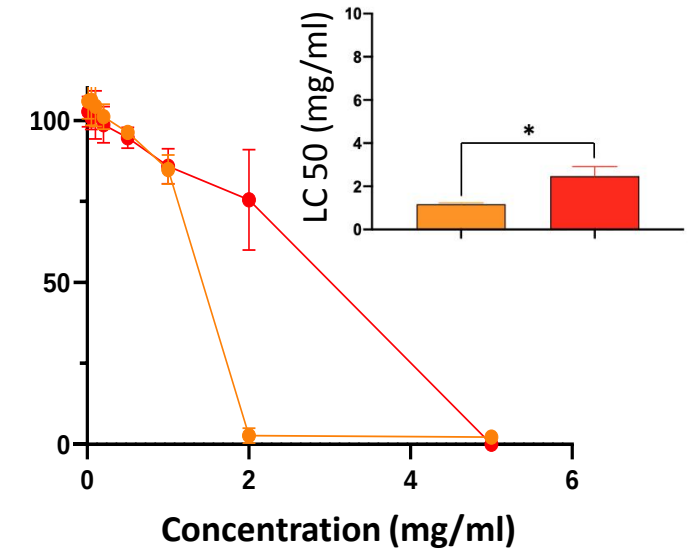


Viability on **HepaRG cells** (n = 3)

24h treatment



28D treatment



- Captex® 50 nm
- Captex® 100 nm

Higher toxicity induced by **LNCs Captex® 50 nm** in both cell lines

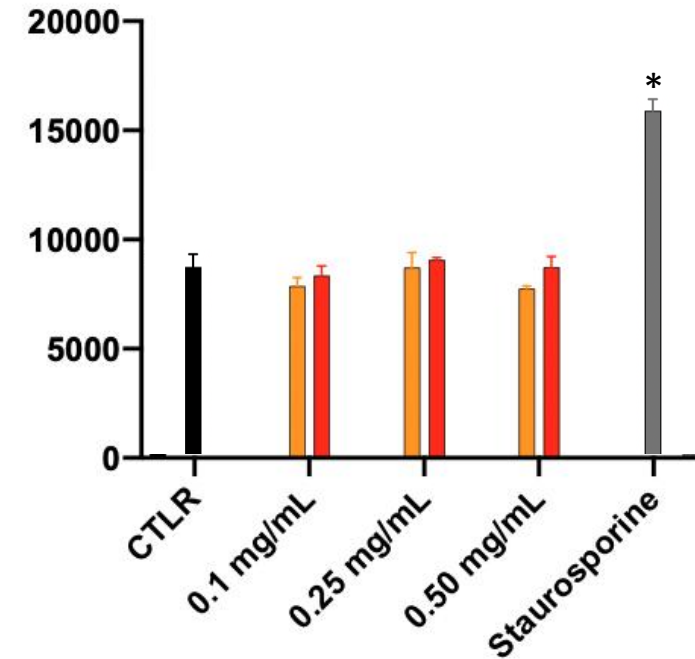
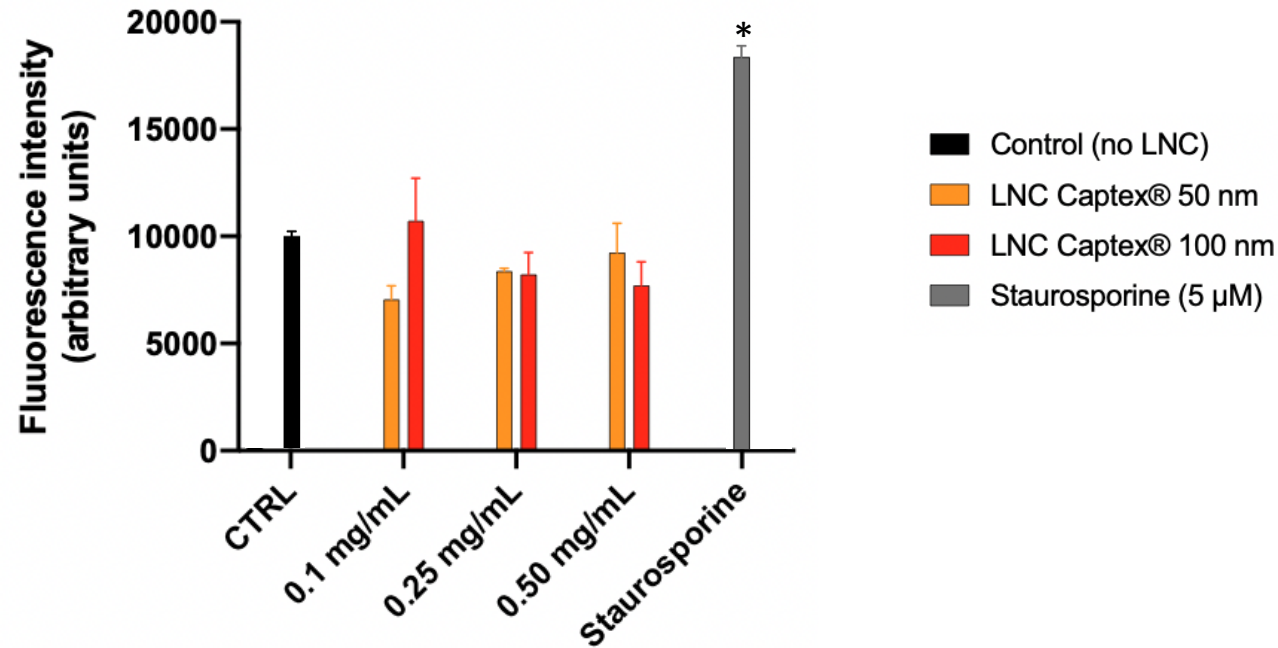
Results: is there a size effect?



Assessment of caspase 3 activity (Ac-DEVD-AMC assay) after 24h of exposure

HepG2 cells (n = 4)

HepaRG cells (n = 3)



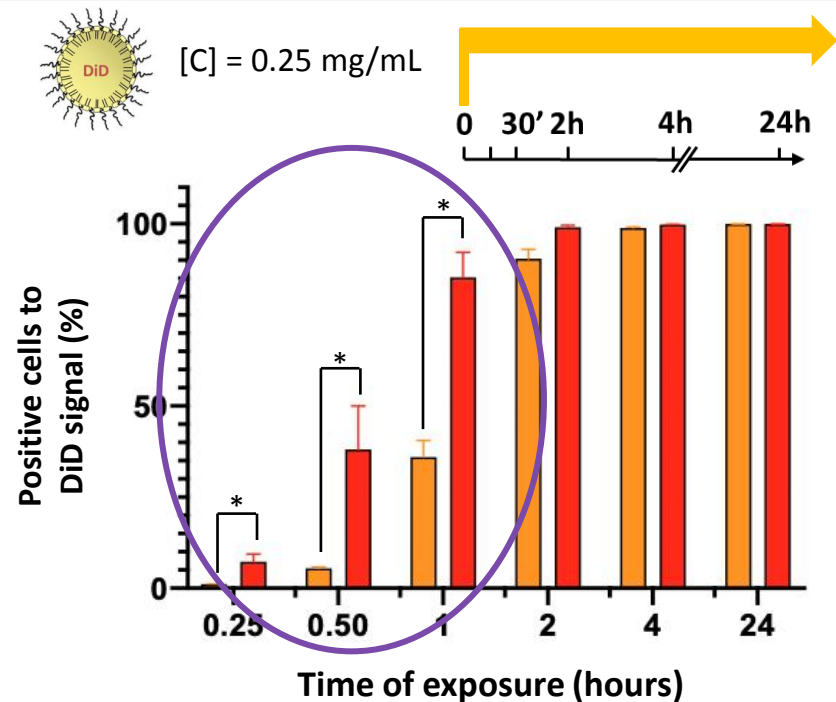
No apoptosis was triggered by LNCs exposure at these concentrations

Results: is there a size effect?

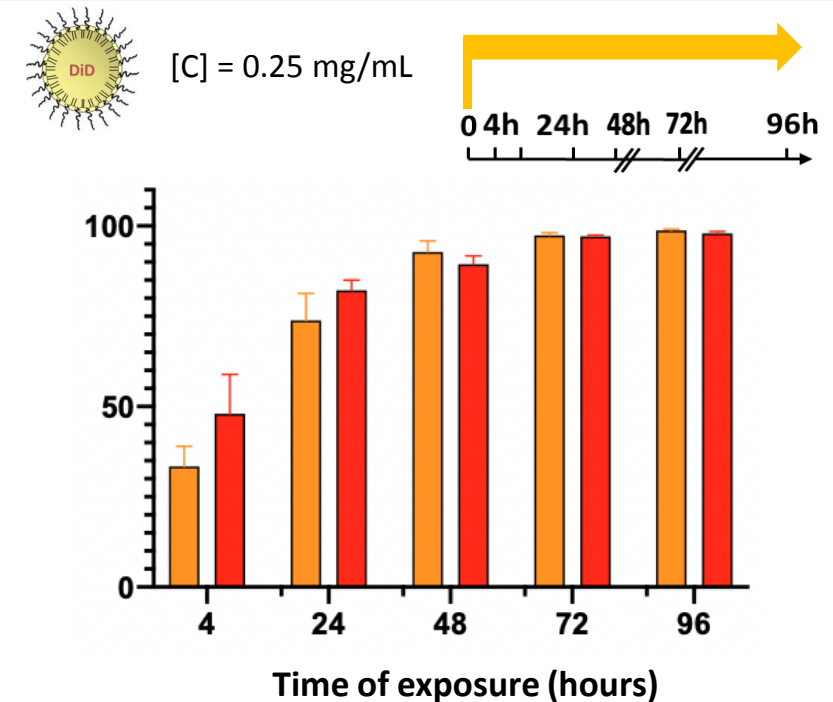


Kinetics of internalization (% of positive cells)

HepG2 cells (n = 3)



HepaRG cells (n = 3)



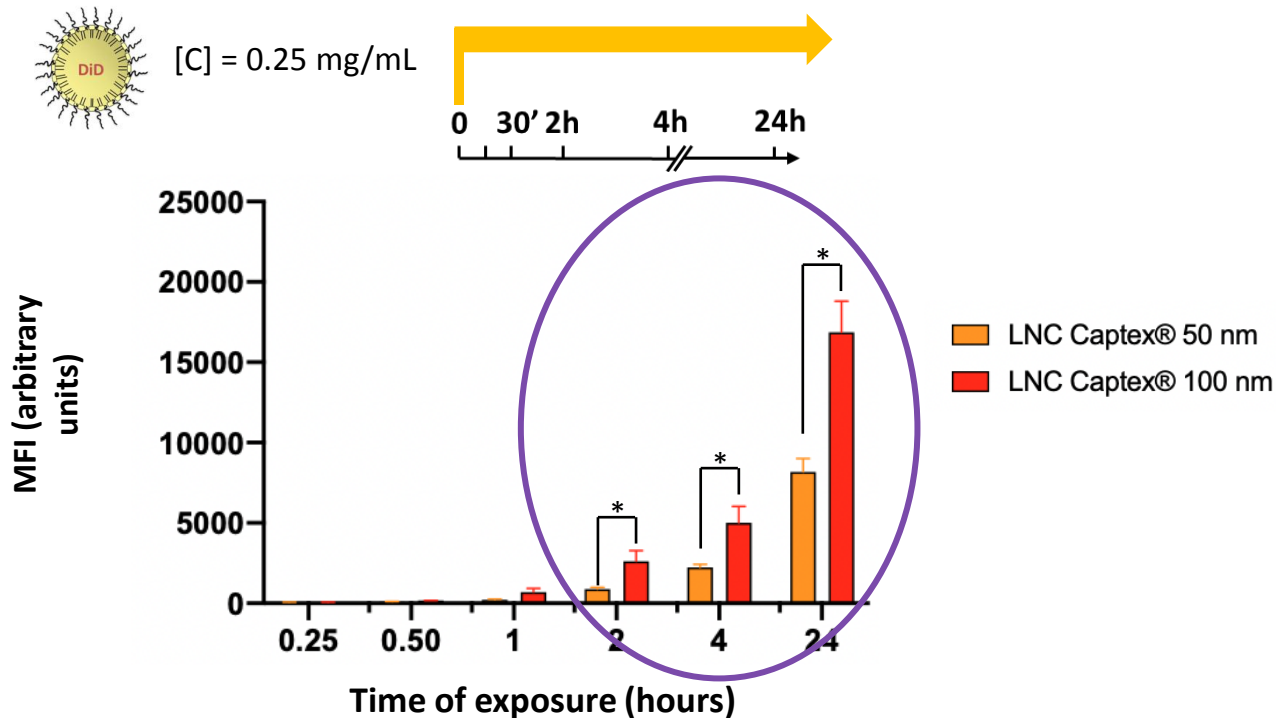
LNCs Captex® 100 nm were internalized faster in HepG2 cells

Results: is there a size effect?

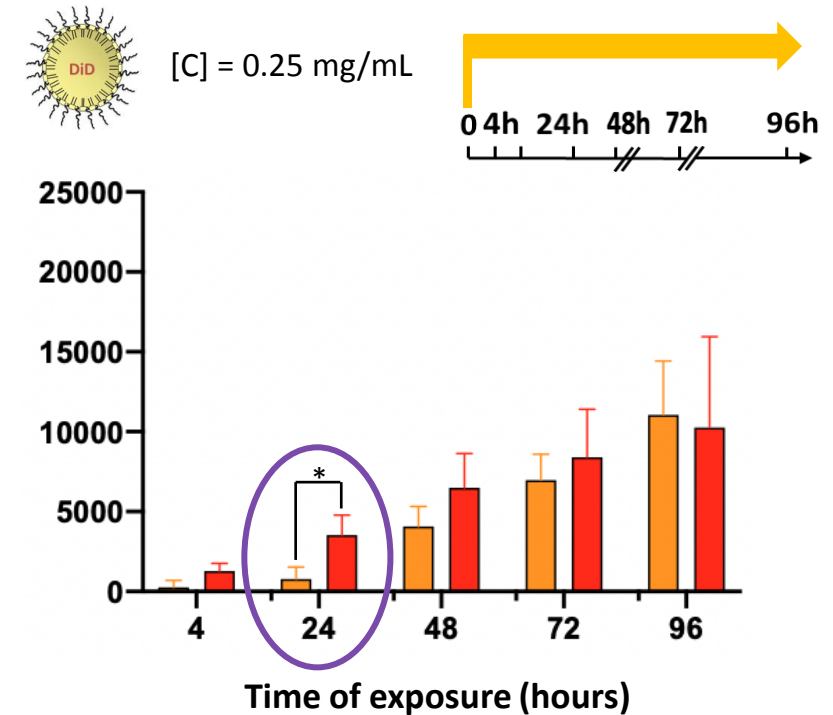


Kinetics of internalization (MFI = mean fluorescence intensity)

HepG2 cells (n = 3)



HepaRG cells (n = 3)



LNC Captex® 100 nm accumulate more than
LNC Captex® 50 nm in HepG2 cells

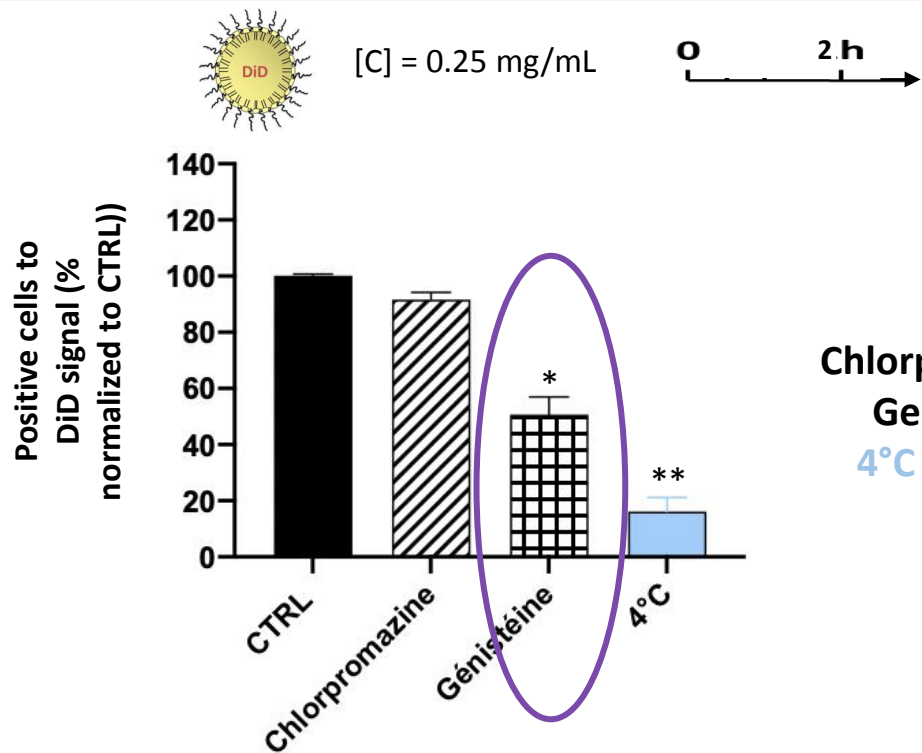
Results: is there a size effect?



Pathways of internalization

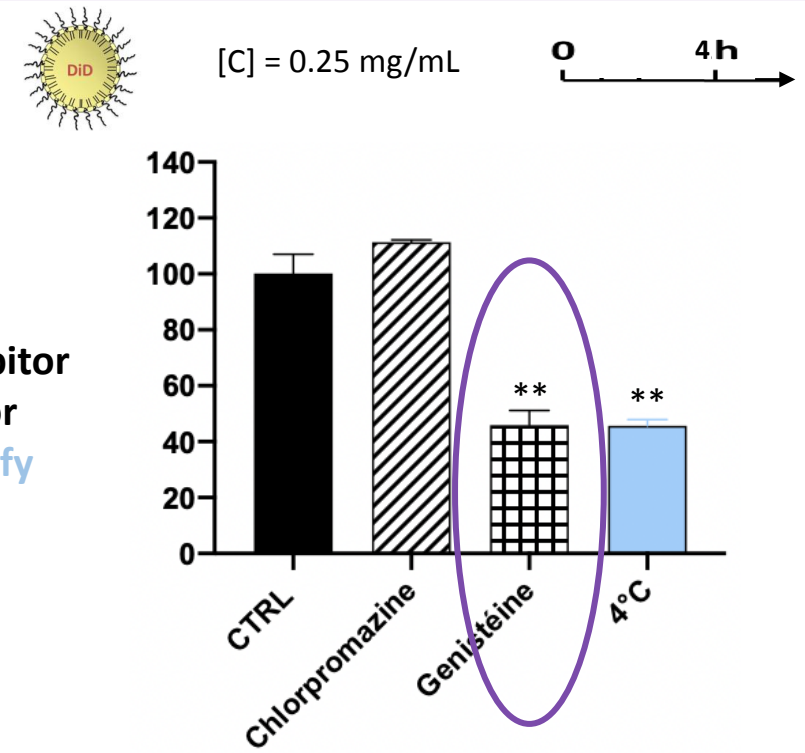
HepG2 cells (n = 3)

HepaRG cells (n = 3)



LNCs 50 nm

Chlorpromazine = clathrin-endocytosis inhibitor
Genistein = caveolin-endocytosis inhibitor
4°C condition = low metabolism and rigidify membranes



LNCs enter mainly via caveolin-mediated endocytosis in both models

Objective



Few studies on
hepatotoxicity



In vitro evaluation of acute and chronic liver toxicity of
LNCs

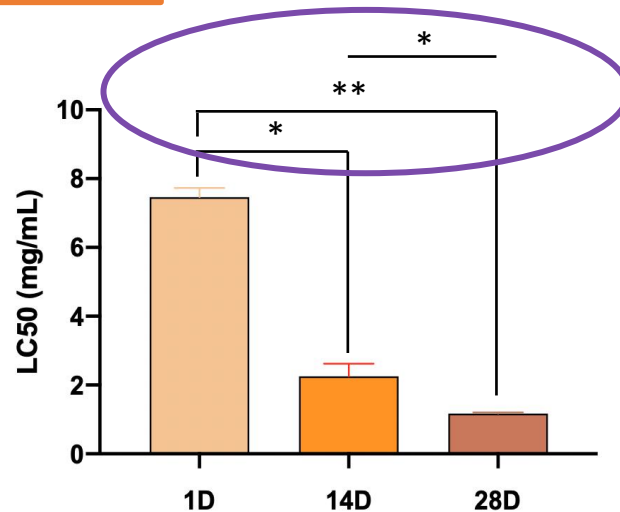
1. Is there a size effect on LNCs's toxicity?
2. Are there **chronic effects** after repeated exposure?

Results: are there chronic effects?

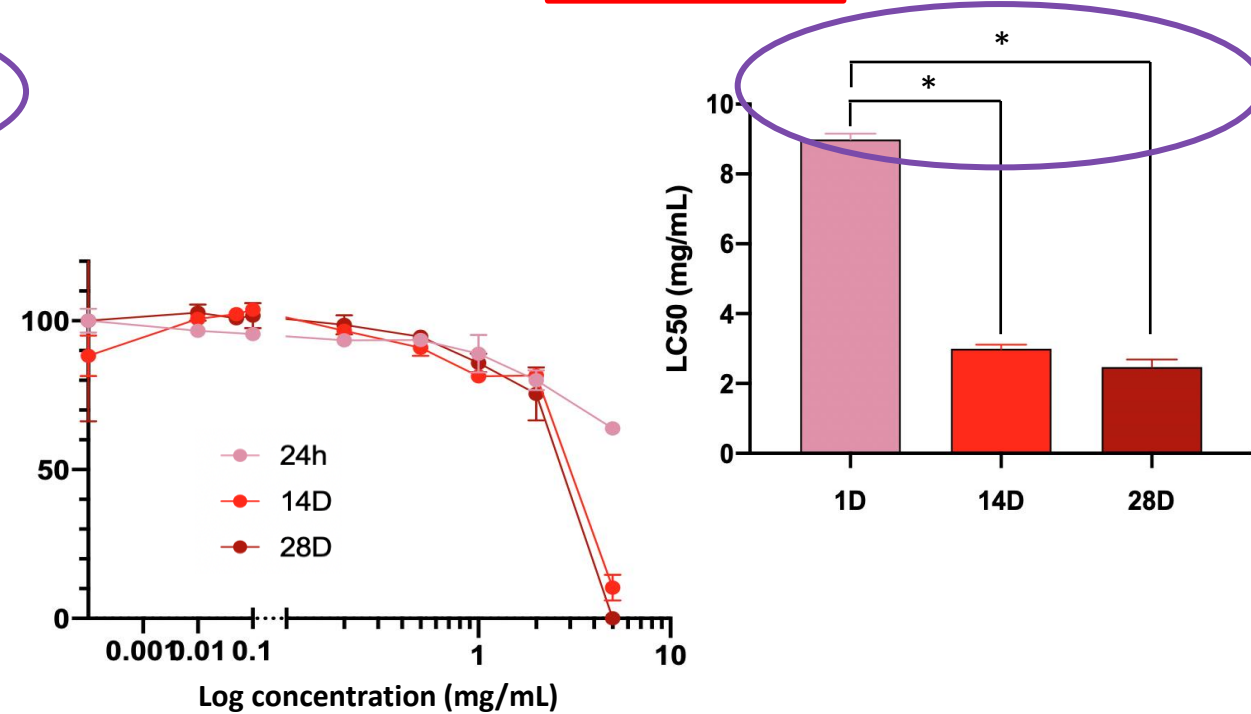


MTT on HepaRG cells (n = 3)

LNCs 50 nm



LNCs 100 nm

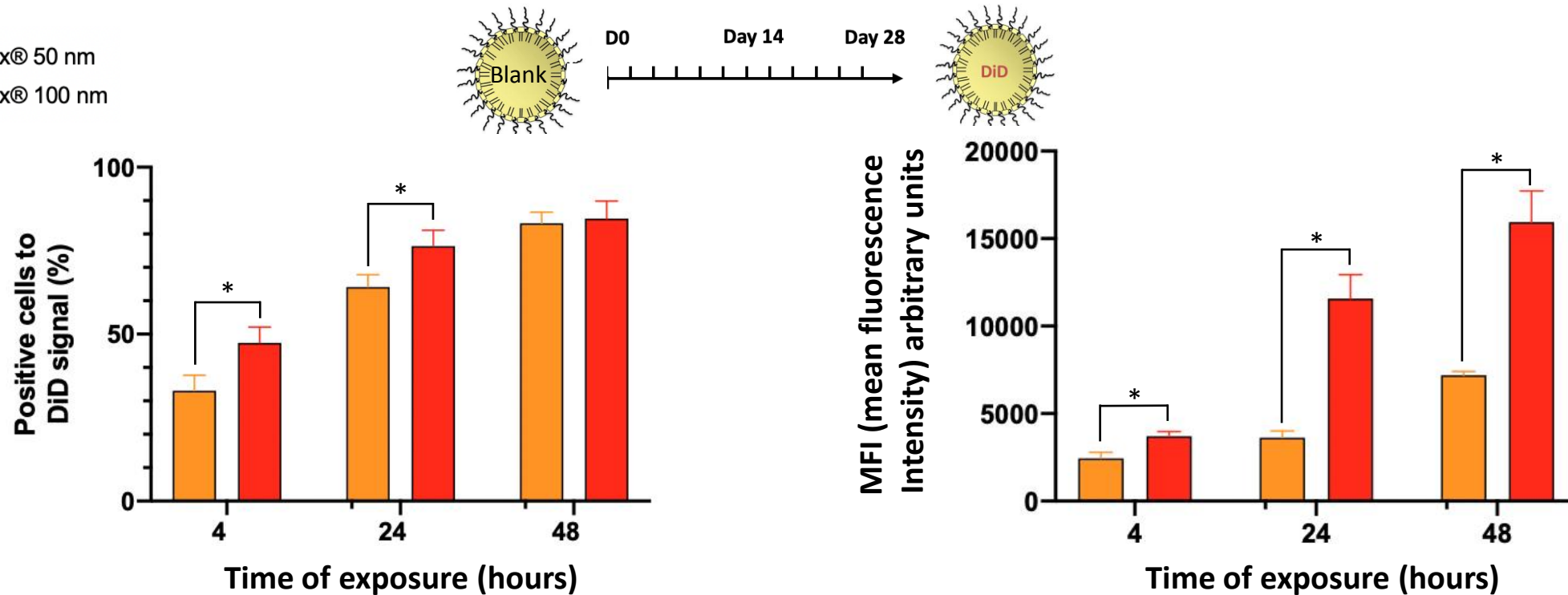


Time effect for 50 nm LNCs – Stability after 2 weeks for 100 nm LNCs

Results: are there chronic effects?



Kinetics of internalization after **28 days of exposure** on HepaRG cells (n = 3)

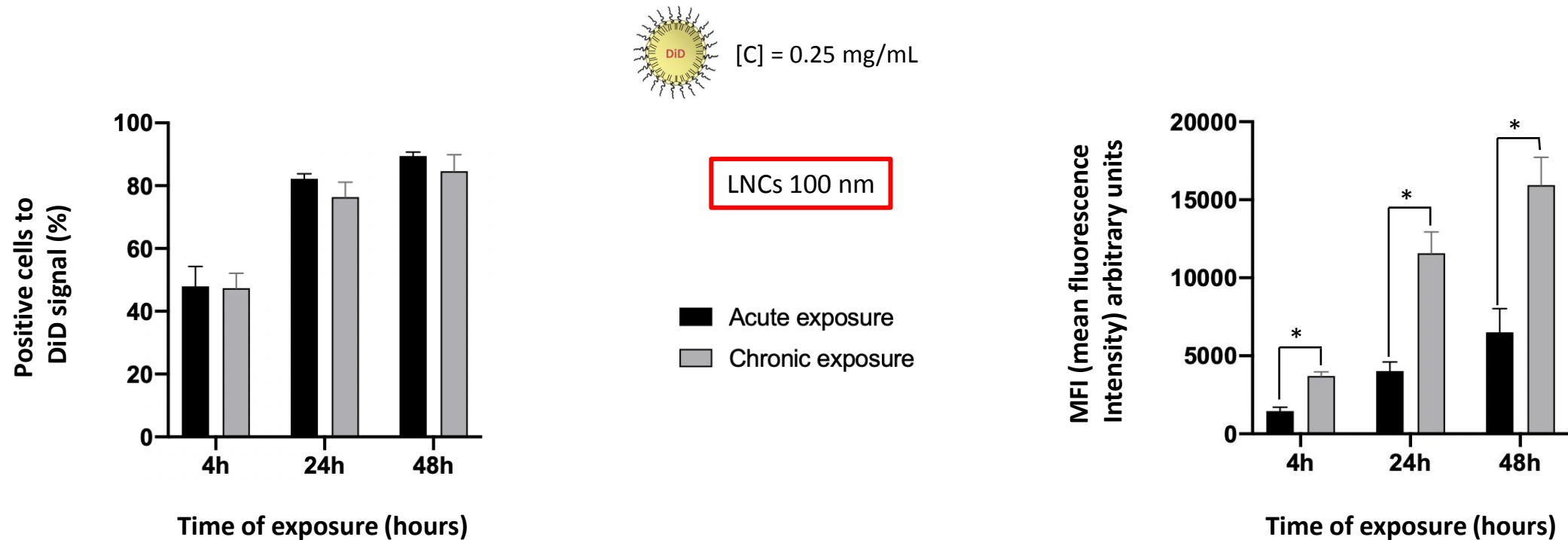


100 nm LNCs are still internalized faster
&
accumulate much more than **50 nm ones**

Results: are there chronic effects?



Comparison of LNCs' internalization **acute vs chronic** on HepaRG cells (n =3)



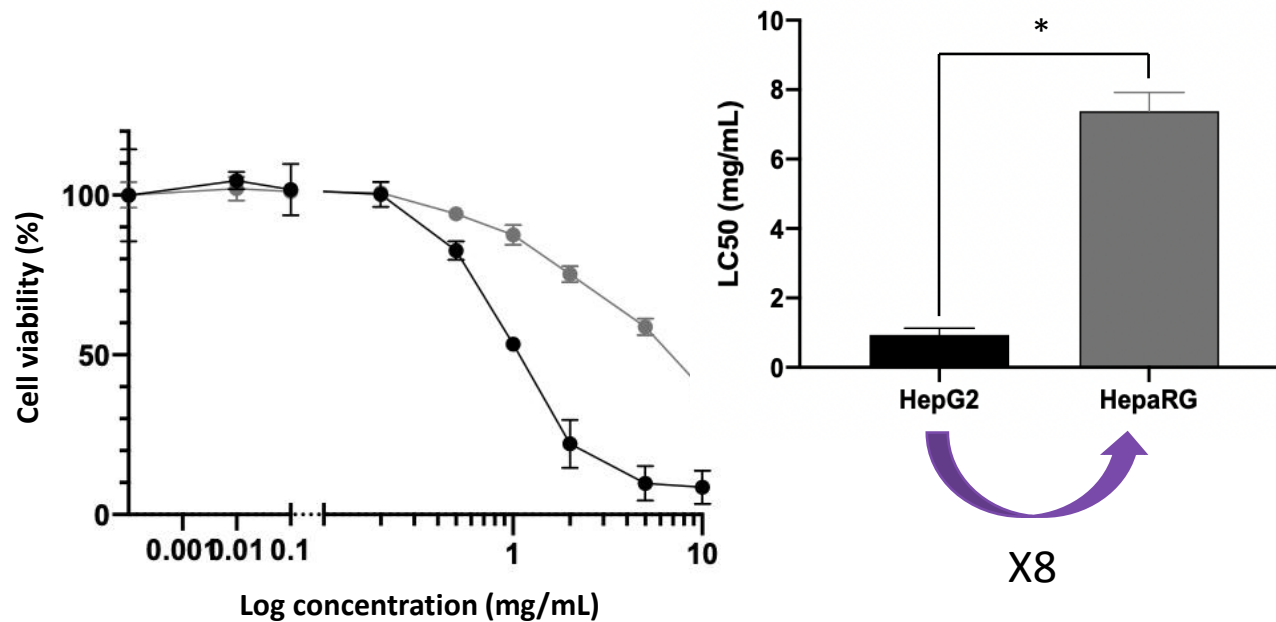
No difference in % of positive cells but much more accumulation after a 28 days chronic exposure

Results: cancerous VS differentiated? (HepG2) (HepaRG)

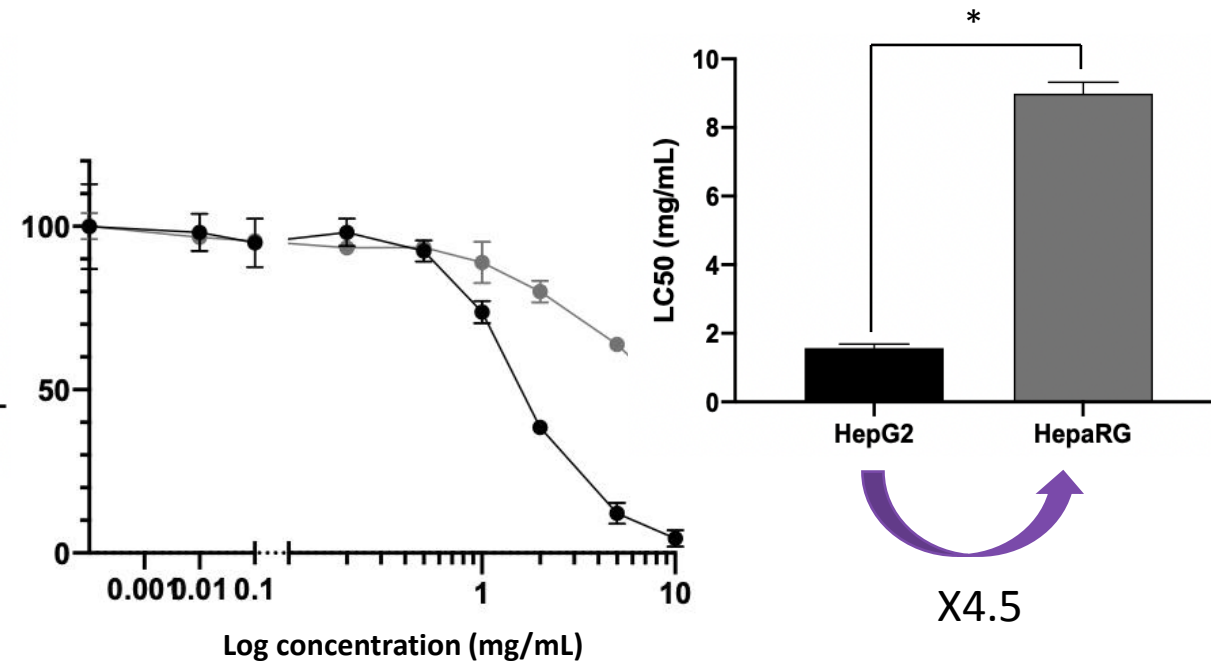


MTT after 24h of exposure (n = 3)

LNCs 50 nm



LNCs 100 nm



Higher toxicity of LNCs on cancerous model, especially 50 nm LNCs

Results: cancerous VS differentiated?

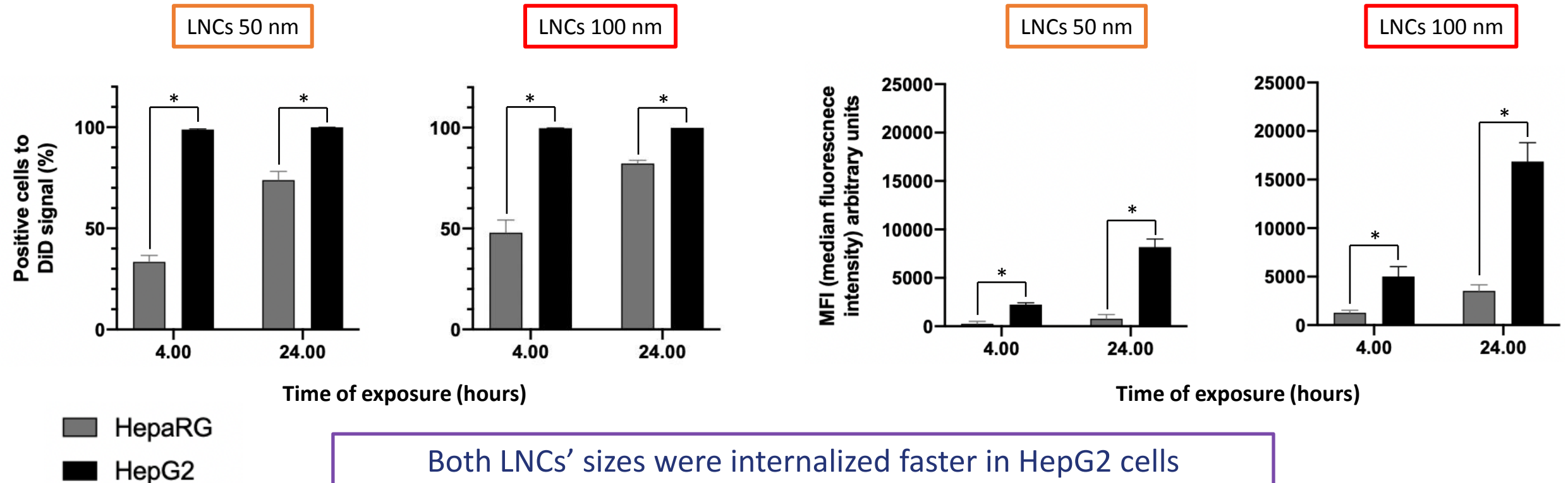
(HepG2) (HepaRG)



Kinetics of internalization (n = 3)

% of positive cells

MFI

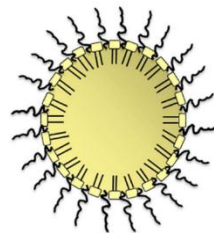


Both LNCs' sizes were internalized faster in HepG2 cells and also accumulated much more

Conclusion / perspectives



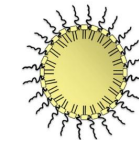
Is there a **size effect**?



100 nm LNCs



Quicker internalization with a lower toxicity



50 nm LNCs

Higher accumulation with a lower toxicity

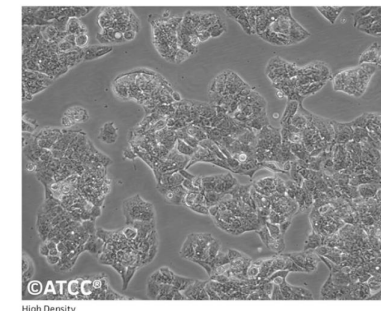
Are there **chronic effects**?

❖ Common points

- 1) No size neither chronic effects for internalization pathways
- 2) No apoptosis & no size effect



HepG2 cells



Acknowledgments



Mint laboratory

**Camille Savary
Emilie Roger
Samuel Legeay
Frédéric Lagarce**



Funding

La ligue contre le cancer 49

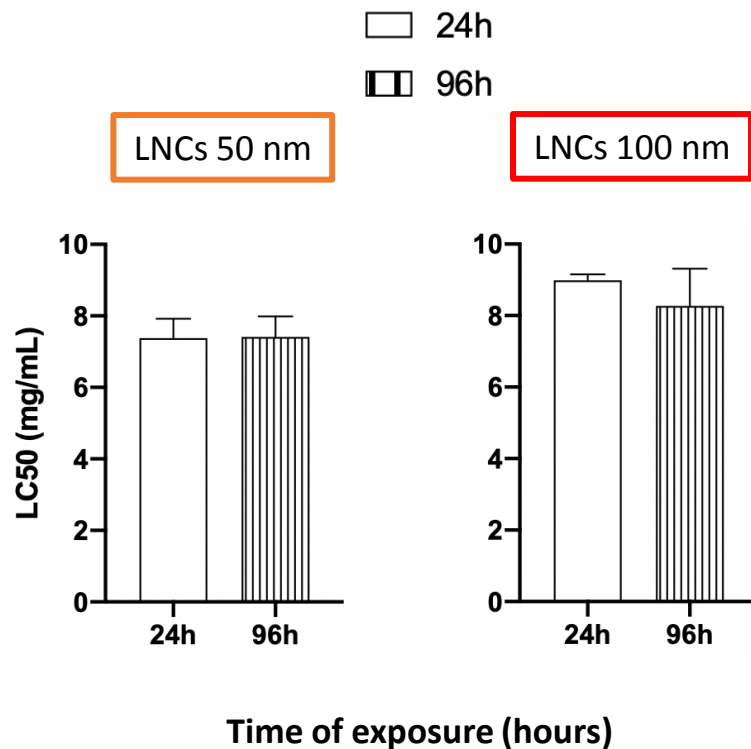
Platforms

Catherine Guillet (PACEM)

Supplementary datas



MTT on HepaRG cells (n = 3)



No difference observed

Pathways of internalization → toxicity of inhibitors by MTT (n = 3)

