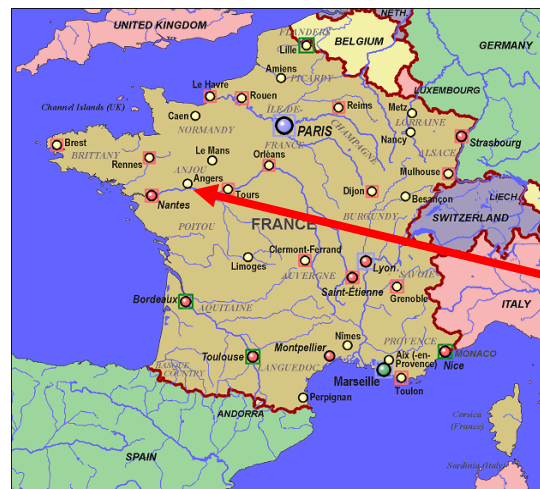


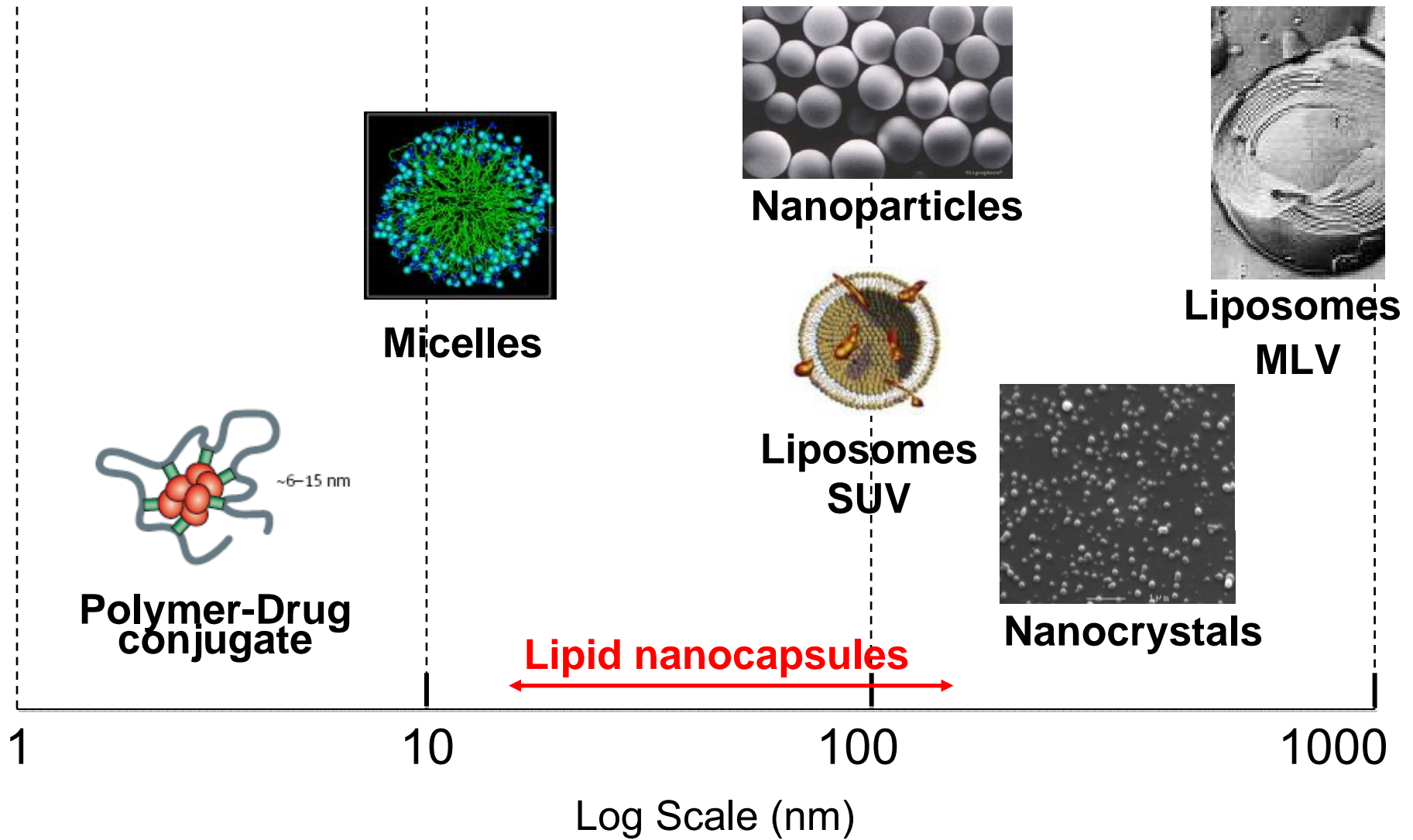
# Lipid nanocapsules in drug delivery

Samuli Hirsjärvi

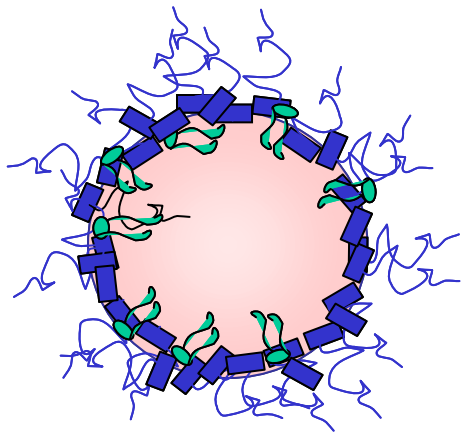
Inserm U646, University of Angers, France



# Nanomedicines

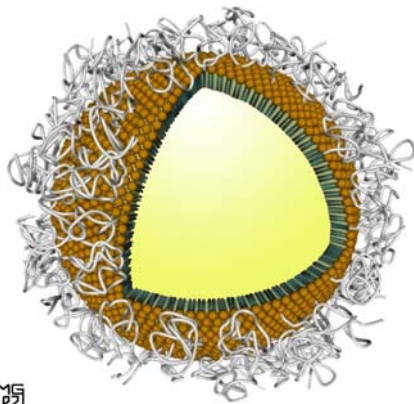


# Lipid nanocapsules (LNC)

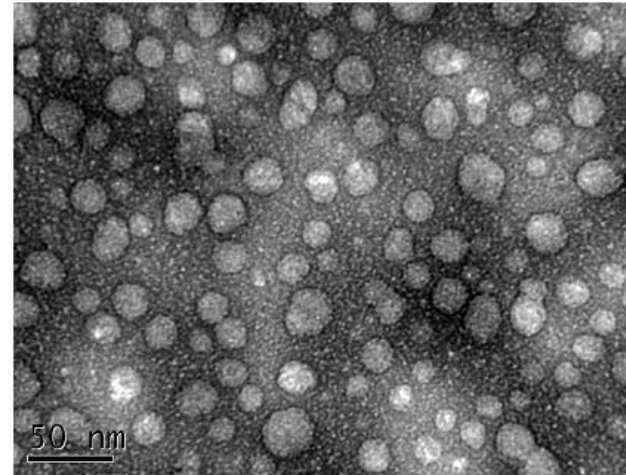


- PEG-hydroxystearate (Solutol®)
- Lecithin (Lipoid®)
- ▲ Triglycerides (Labrafac®)

- Lipophilic drugs in the oily core
- Hydrophilic drugs encapsulated as a microemulsion in the oily core



- Huile
- Phospholipide
- Surfactant pegylé



SCIAM, University of Angers

# Properties of lipid nanocapsules

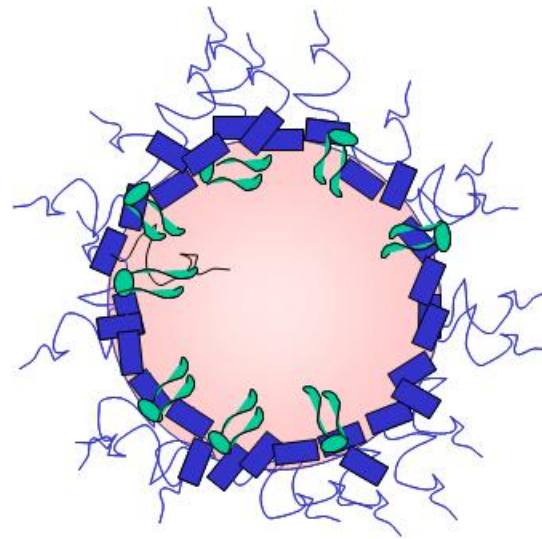
Simple preparation,  
GRAS excipients

Stealth properties

Adjustable size  
20-150 nm

No organic solvents, no  
high energy needed

Easy scale up possible



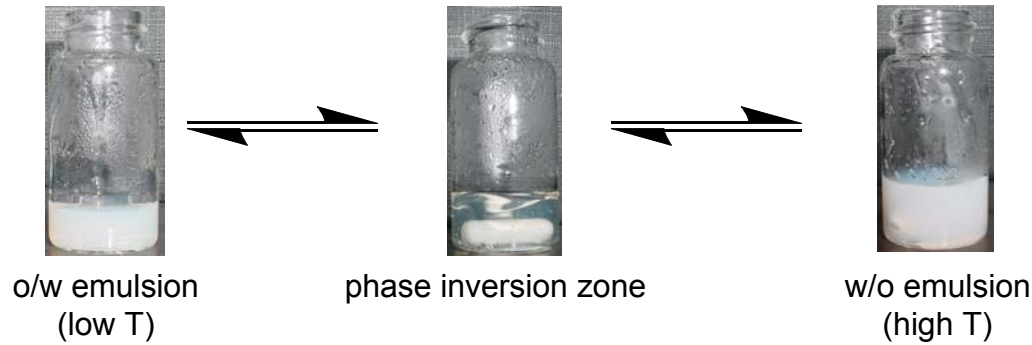
Cytostatic  
action *in vitro*  
and *in vivo* to  
glioma cells

Capacity to  
inhibit P-gp

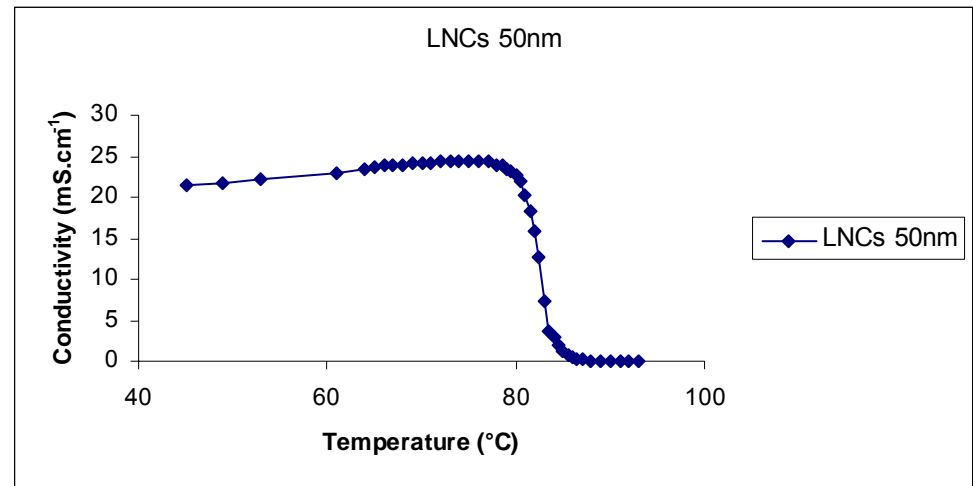
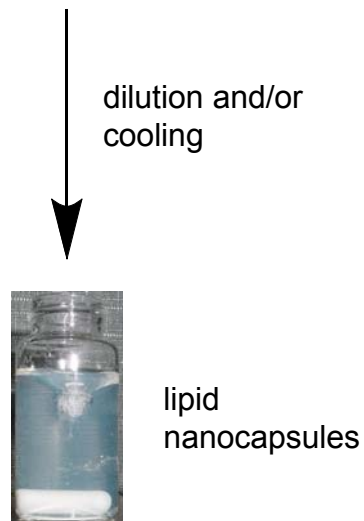
Dispersion stability > 1 year

(Huynh *et al.*, 2009)

# Fabrication process

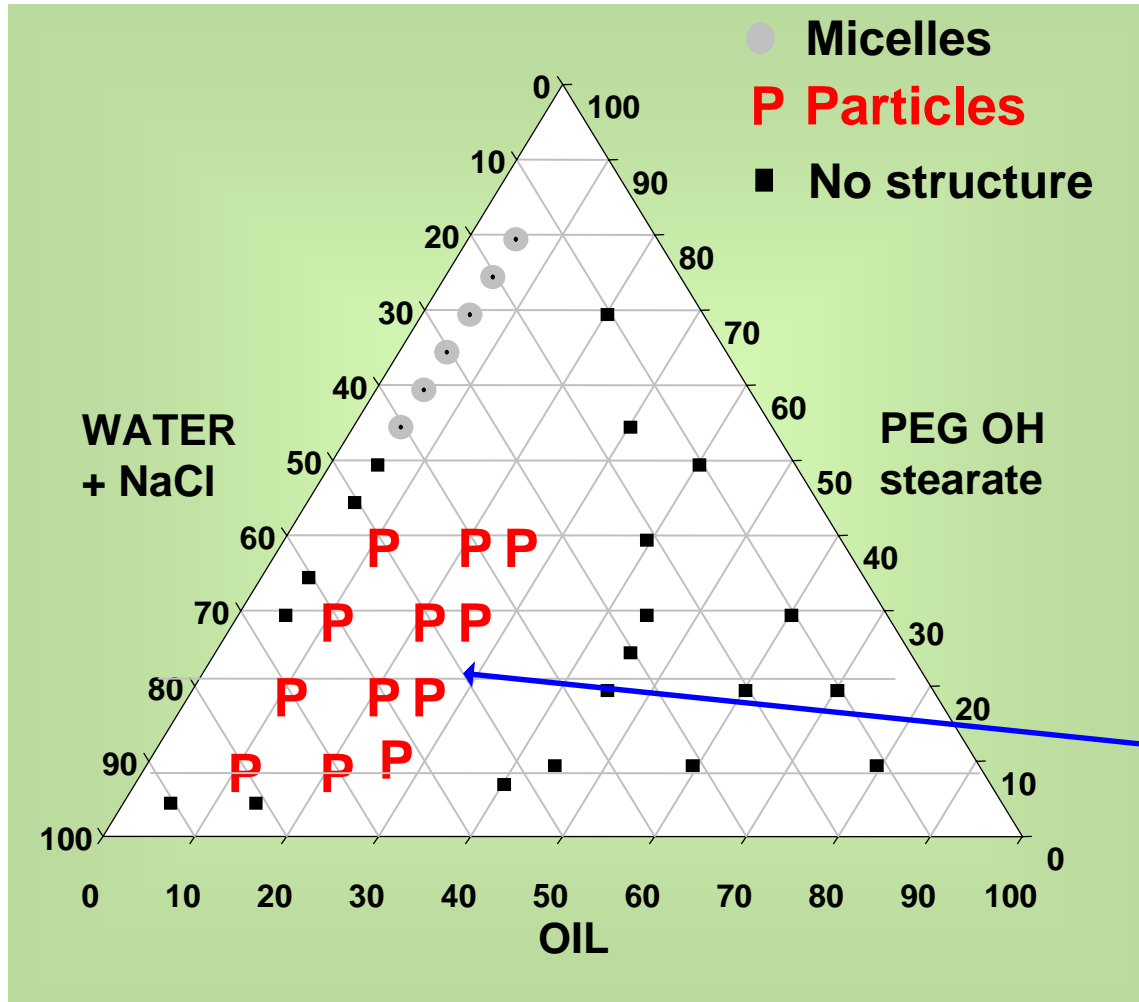


Low-energy method based on phase inversion induced by temperature change



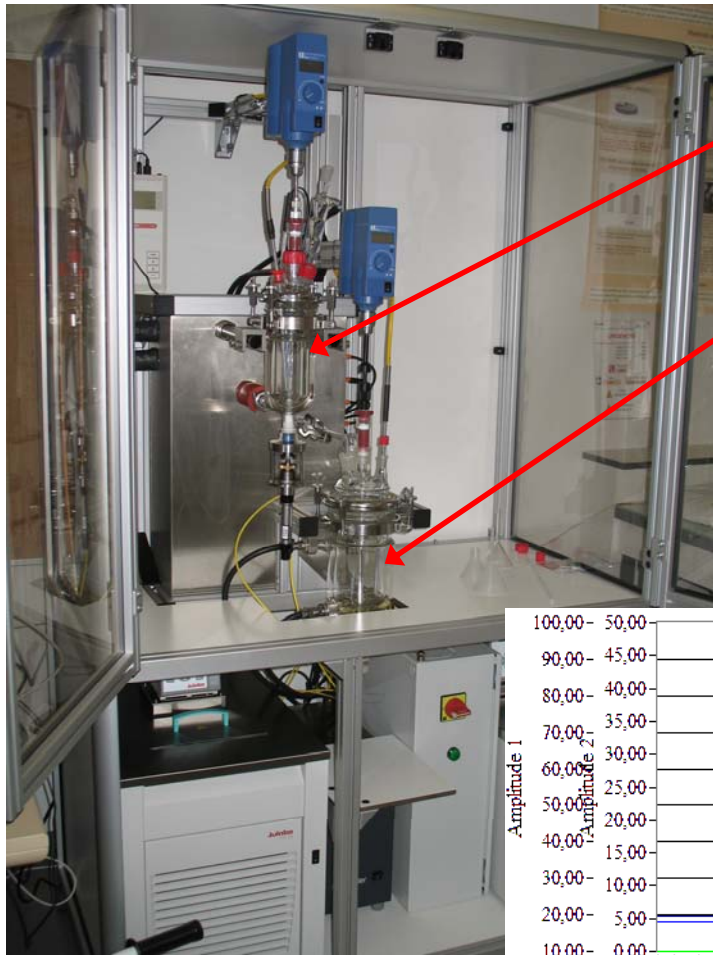
(Heurtault *et al.*, 2002)

# Formulation of LNC



(Heurtault *et al.* 2003)

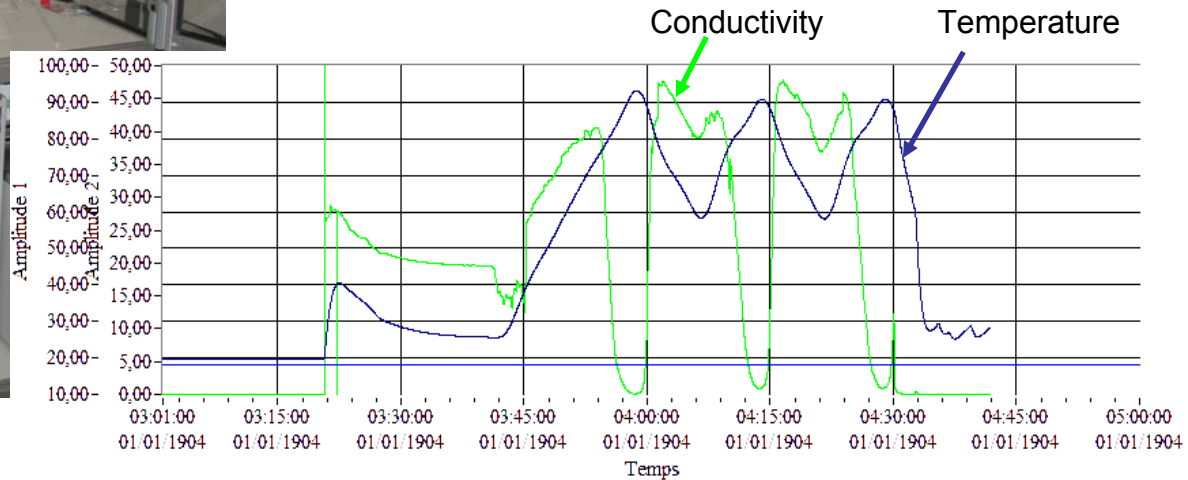
# Pilot-scale fabrication






Temperature cycles

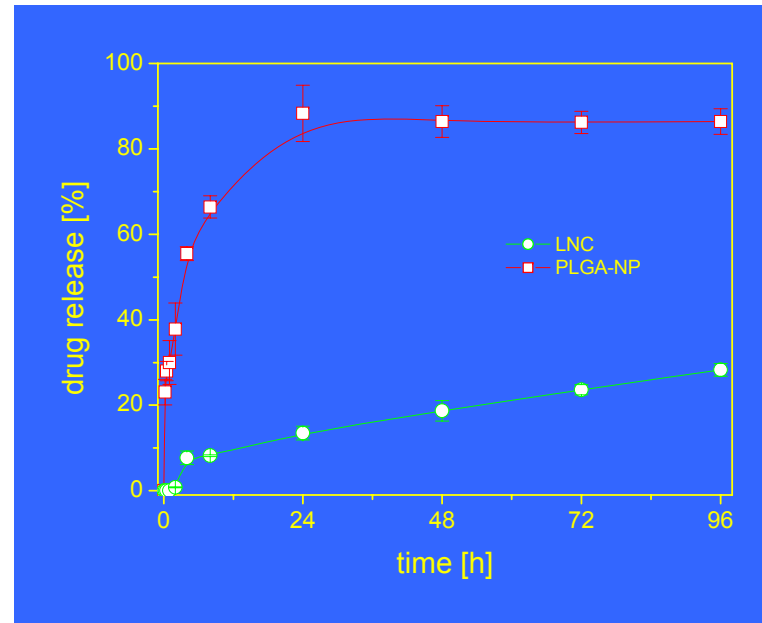
Dilution with cold water

**Batch sizes up to 50x (50 g of LNC)**



Température masse=F[Temps écoulé]   
Température masse=F[Temps écoulé]   
Conductivité=F[Temps écoulé (s)] 

# Release profile from LNCs



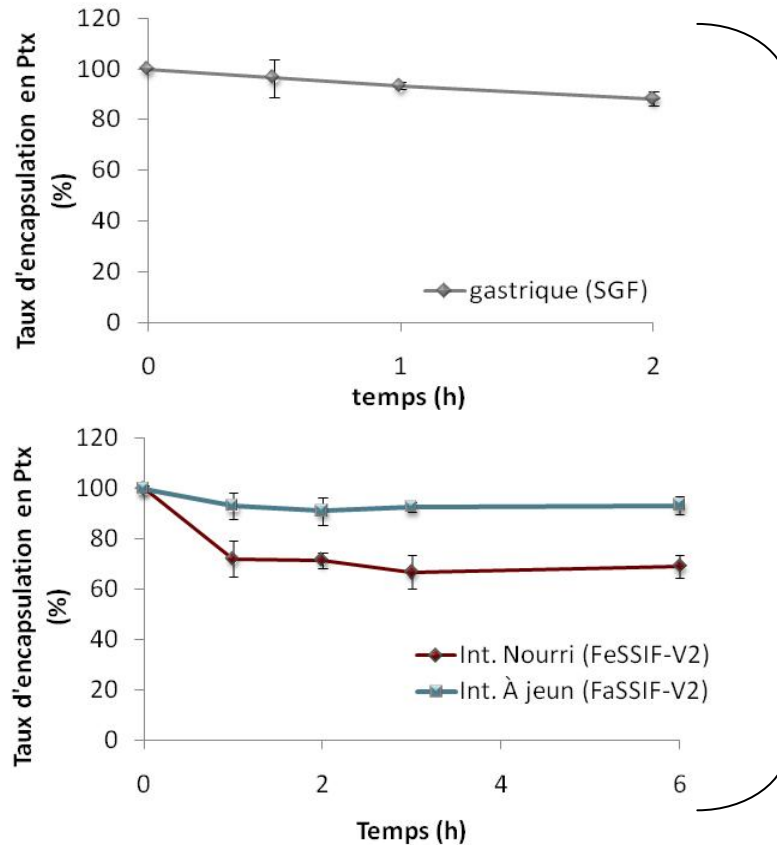
**Same loading (amiodarone), different kinetics:**  
polymeric nanoparticles (PLGA)

⇒ **matrix**

lipid nanocapsules

⇒ **reservoir + membrane**

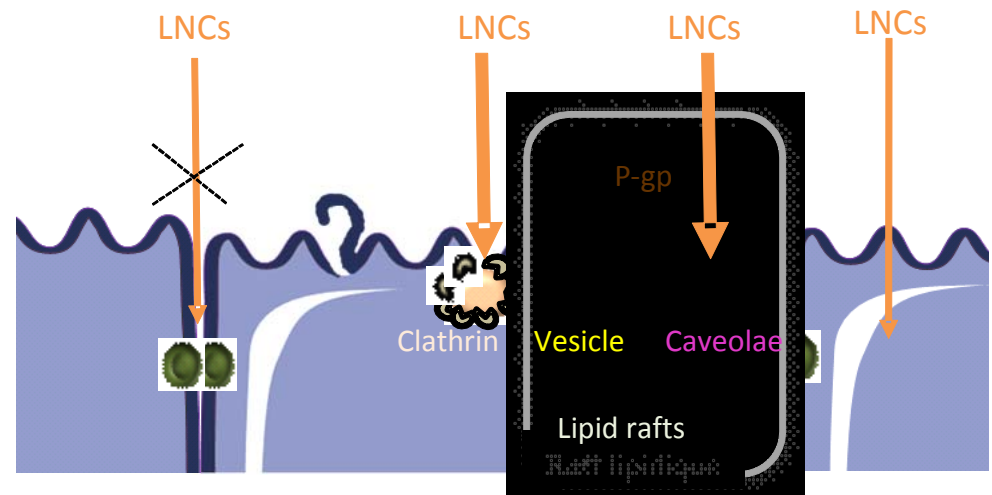
# GI stability of LNC and transport across intestinal epithelium



Gastric fluid: size remained stable; 12% paclitaxel released

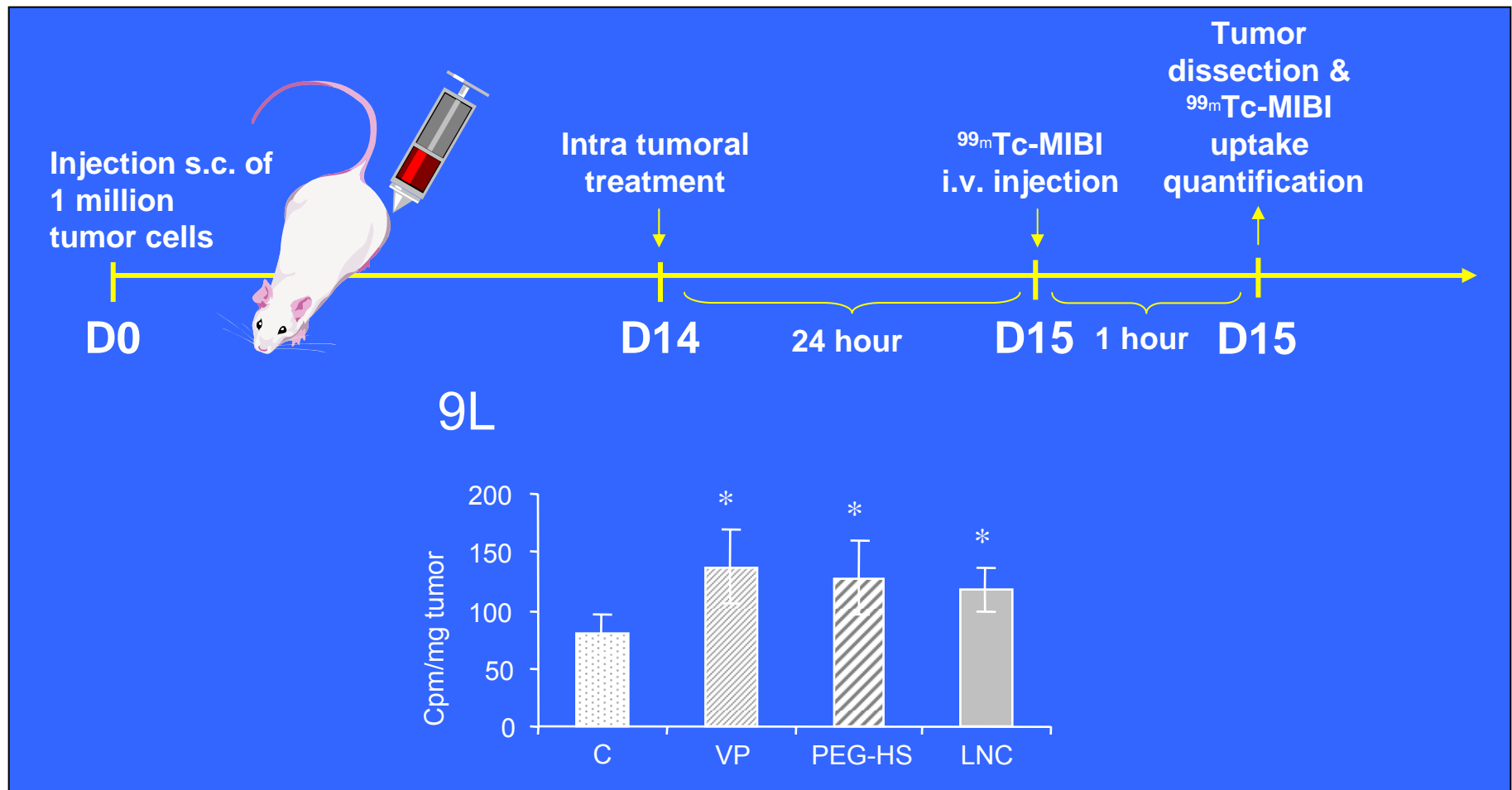
Intestinal fluid: size stable; paclitaxel released: 6.5% in fasted state, 30% fed state

(Roger *et al.*, *Int. J. Pharm.* (2009) 379, 260)



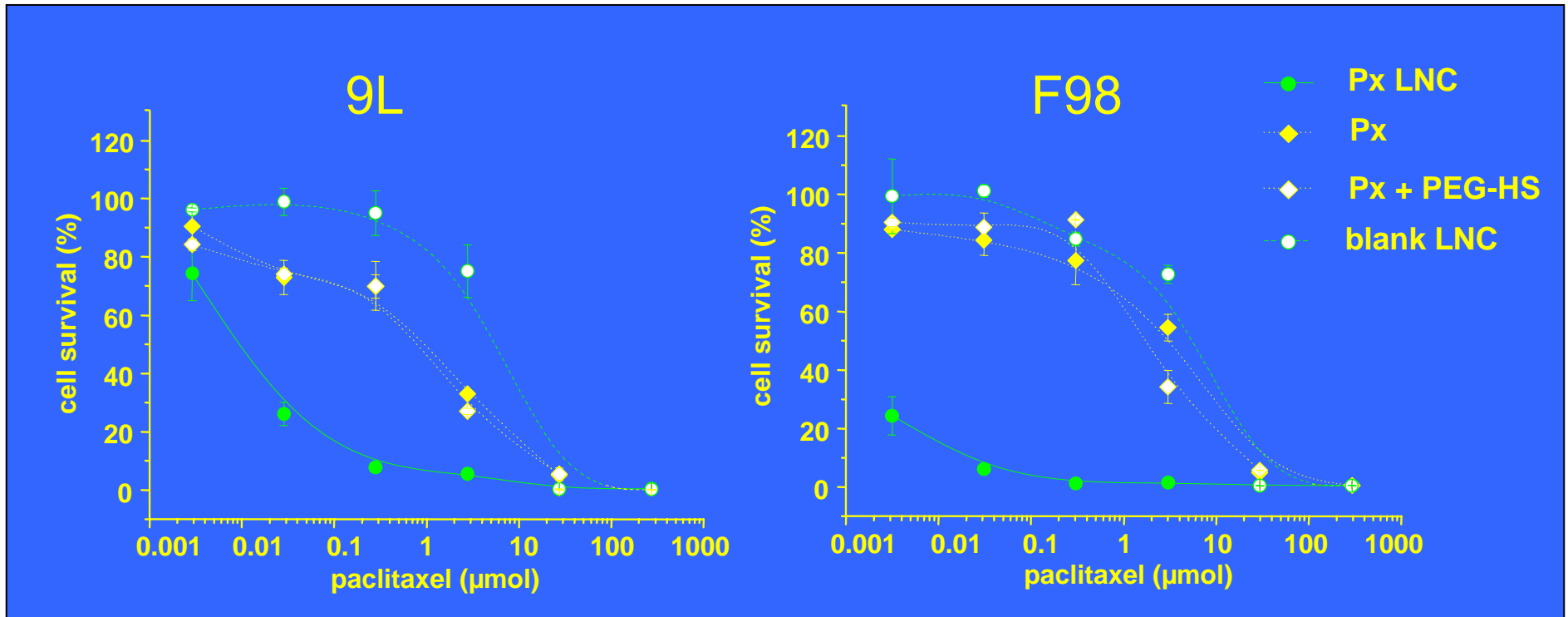
3.5-fold transport of paclitaxel across Caco-2 cells compared to Taxol® (Roger *et al.*, *J. Control. Release* (2009) 140, 174)

# Tumor uptake of $^{99m}\text{Tc}$ -MIBI is improved by LNC and classical P-gp inhibitors *in vivo*



→ LNC inhibit MDR phenomenon *in vivo*

# Evaluation in cell culture (glioma cells)

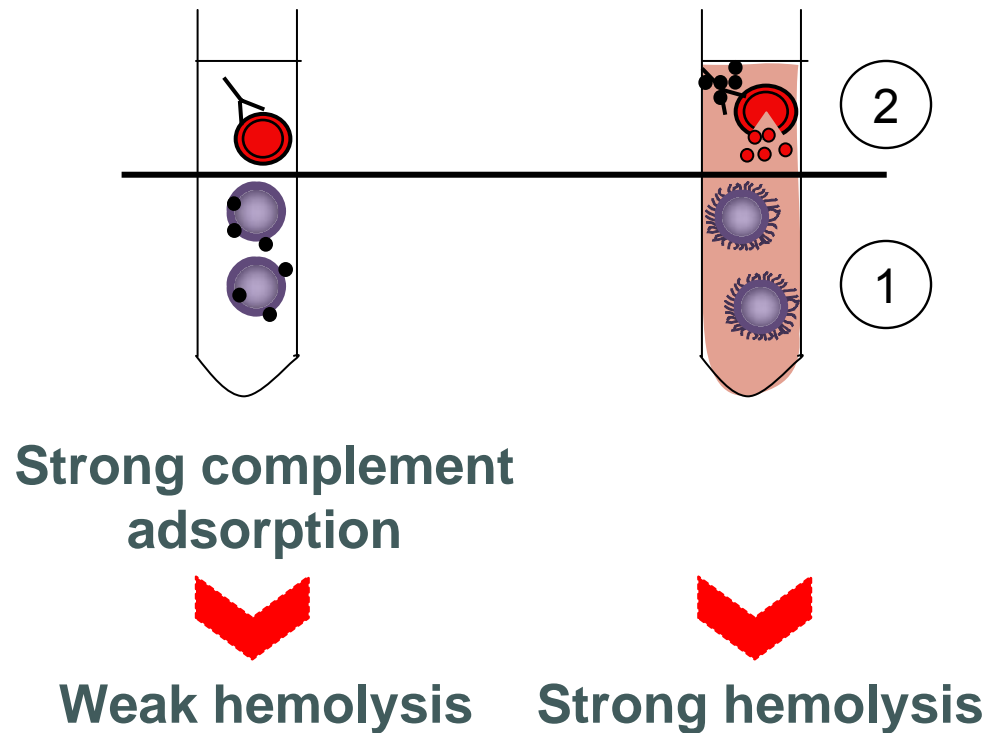
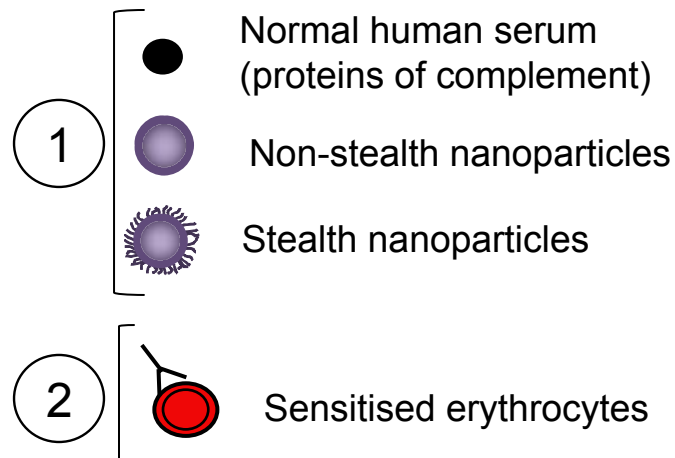


**9L** Px LNC induce 80% cell death at  $2 \cdot 10^{-1}$  mM (>100X)  
Taxol induces 80% cell death at 20 mM

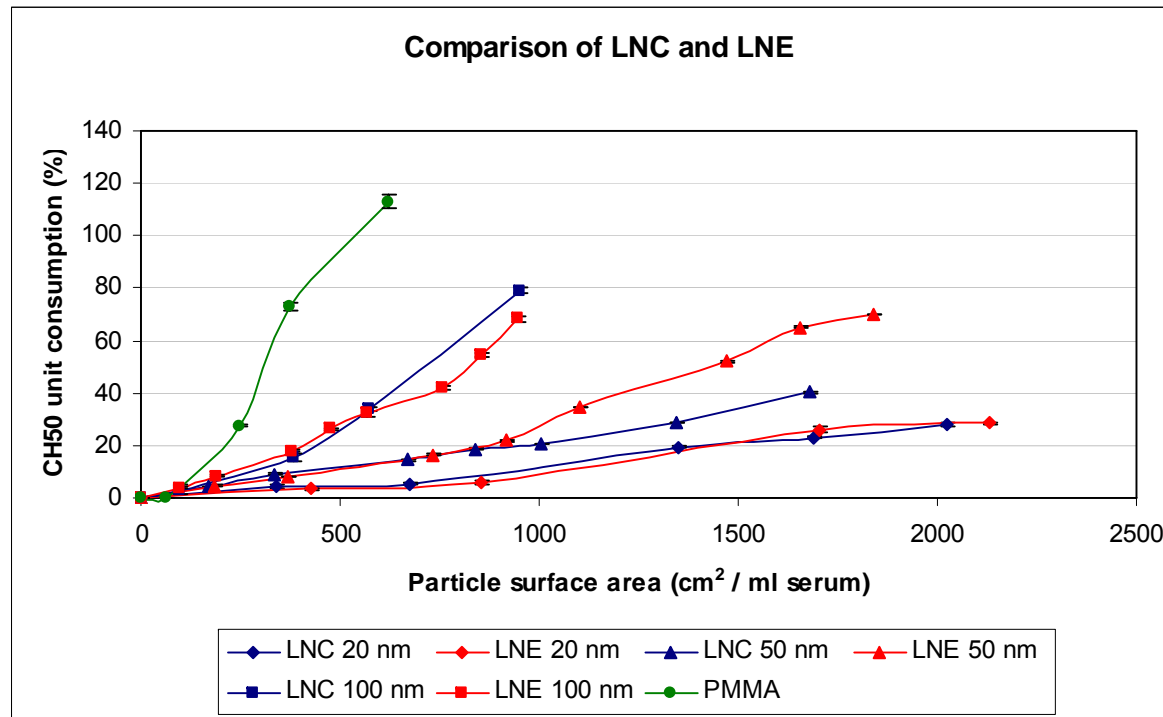
**F98** Px LNC induce 80% cell death at  $2 \cdot 10^{-2}$  mM (>1000X)  
Taxol induces 80% cell death at 20 mM

# Activation of the complement system

## CH50 test:



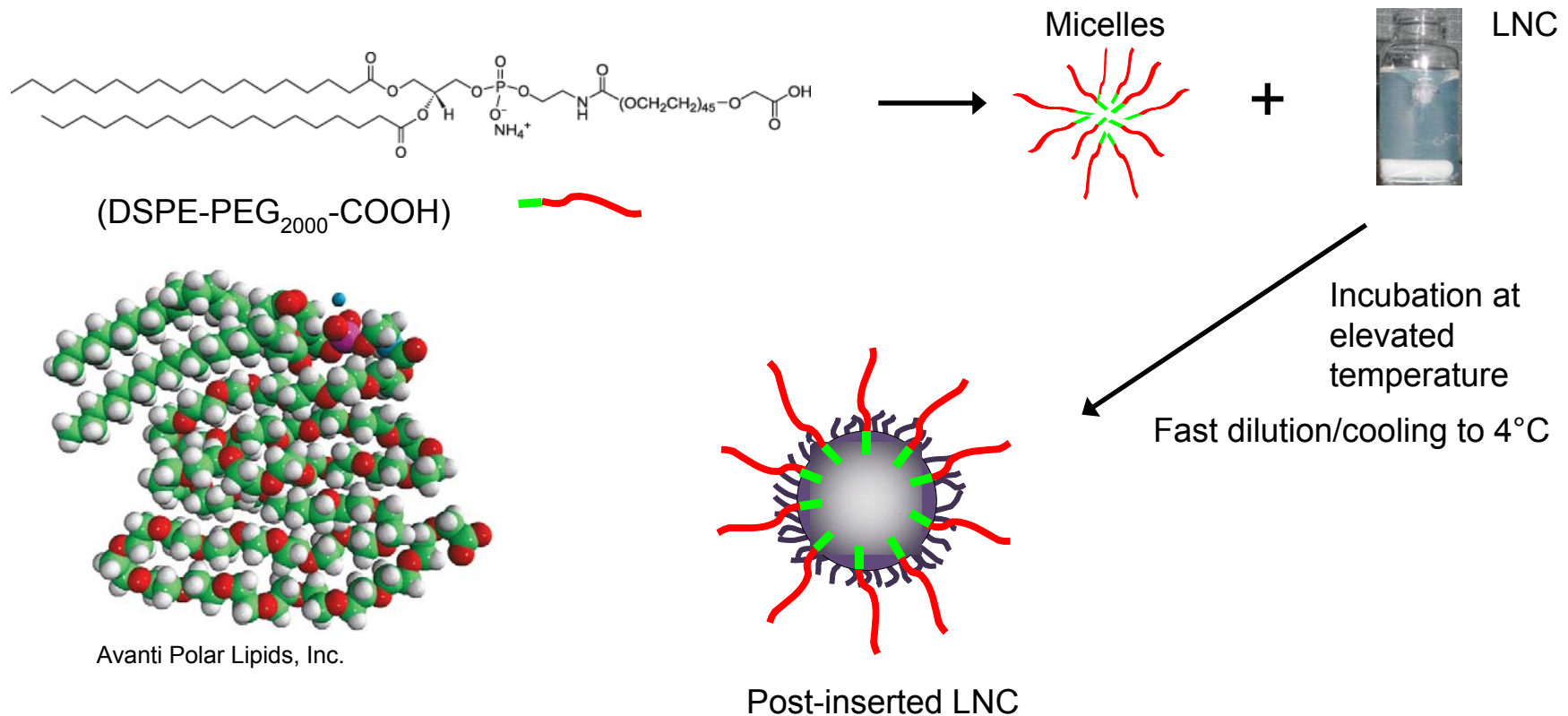
# Activation of the complement system



- Lipid nanocapsules (LNC) and lipid nanoemulsions (LNE) activate little the complement system → good stealth properties
- Complement activation size dependent

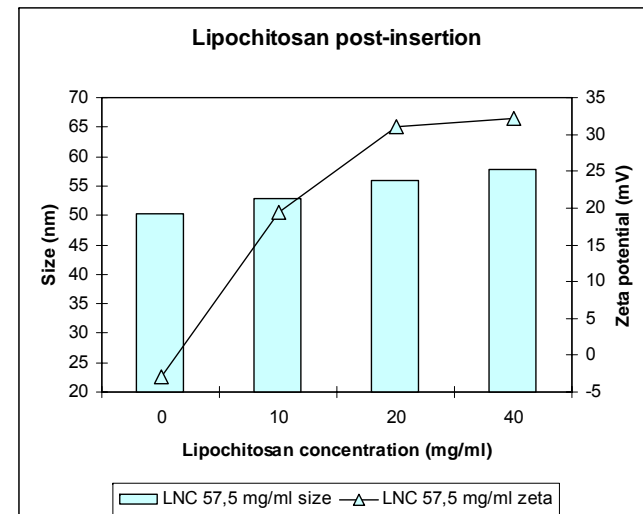
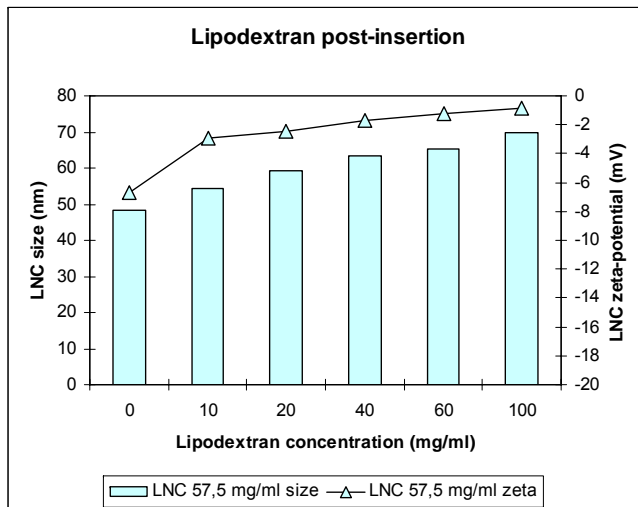
# Surface modification by post-insertion

- LNC = "soft particles"

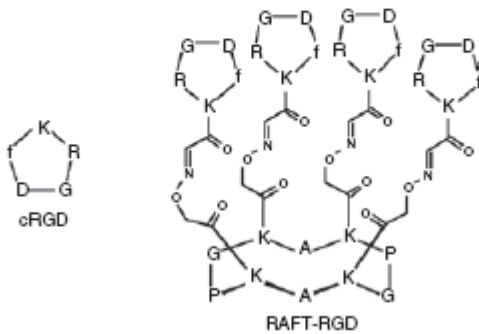


# Surface modification by post-insertion

	LNC size (nm)	Polydispersity index	Zeta-potential (mV)
Starting lipid nanocapsules	50	0.026	-5
DSPE-PEG <sub>2000</sub> -COOH inserted	57	0.062	-42
"Lipodextran" inserted	59	0.045	-2
"Lipochitosan" inserted	56	0.066	+31

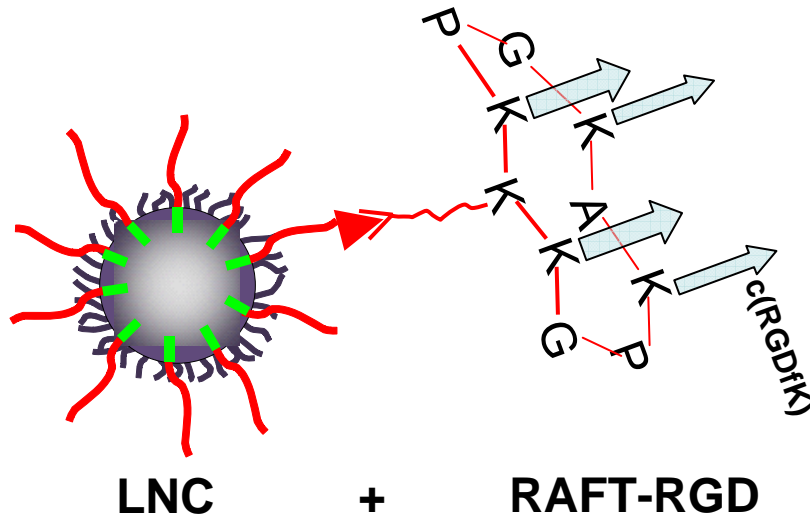


# Attachment of a targeting ligand



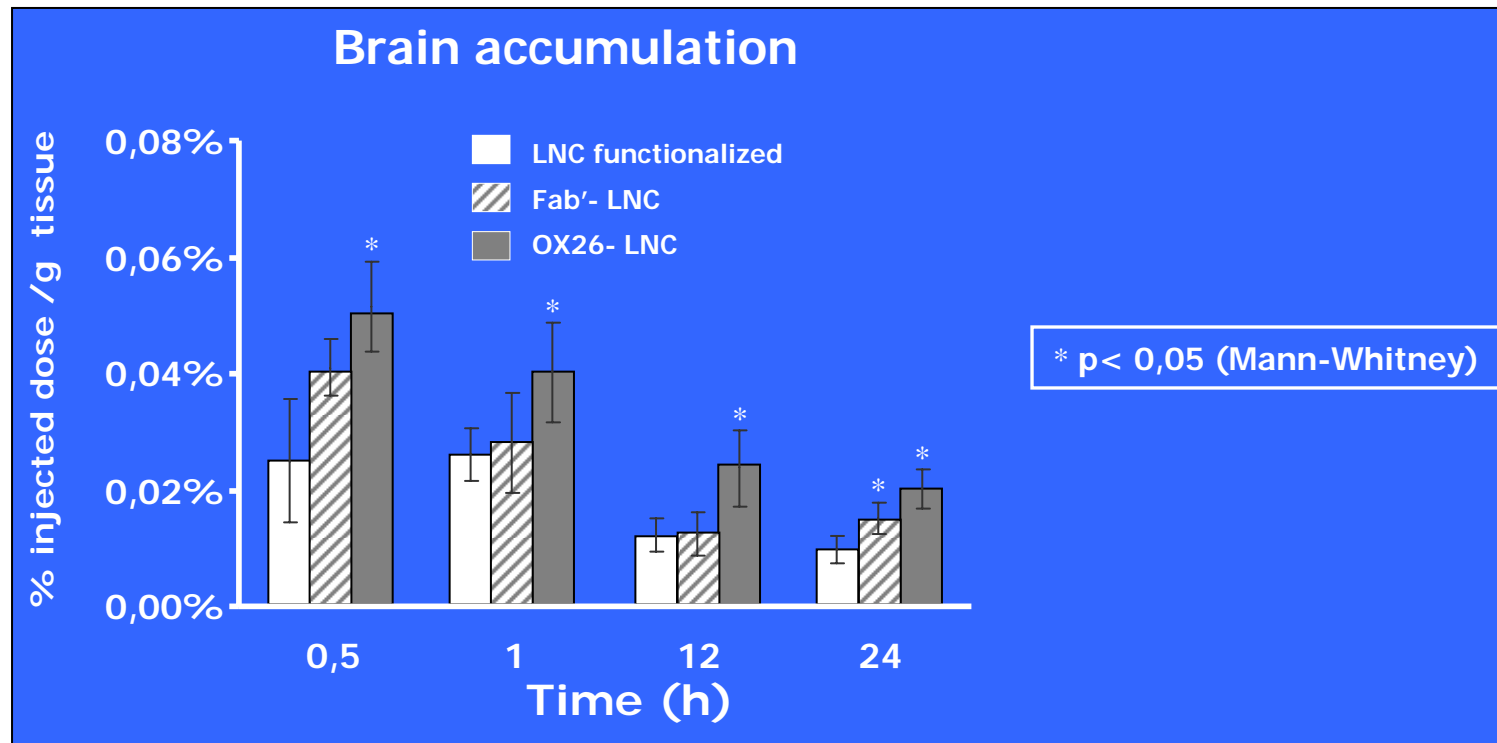
- RGD peptide binds to  $\alpha_v\beta_3$  integrin on tumour cell surface
- RAFT (Regioselectively Addressable Functionalized Template): multimeric presentation of ligands

(Boturyn *et al.*, JACS (2004) 126, 5730)



	Size (nm)
LNC	50
LNC RAFT-RGD	61

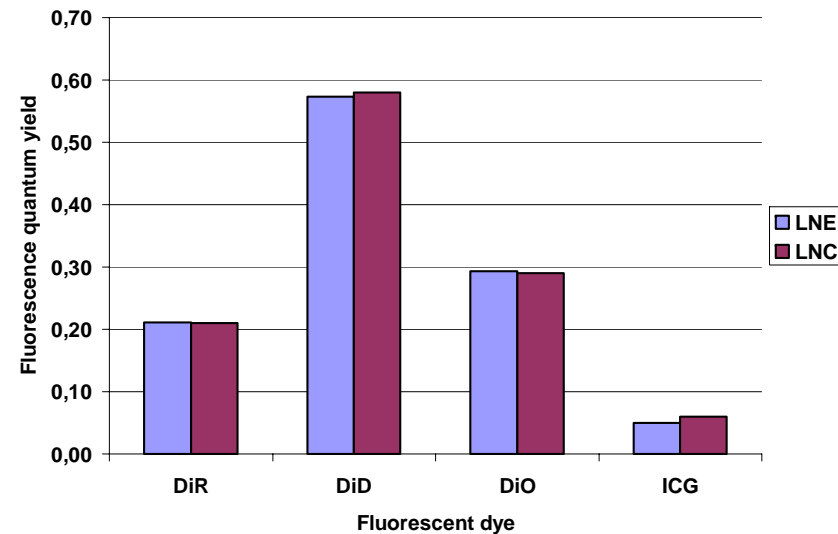
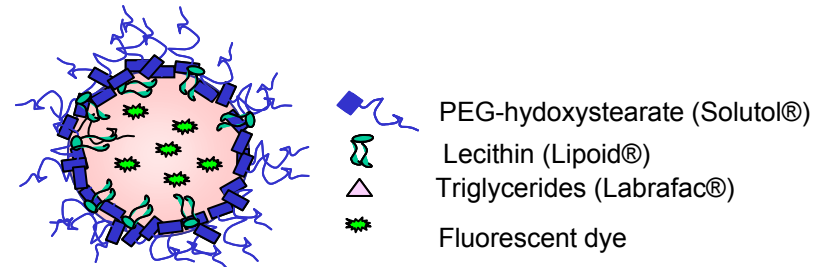
# Biodistribution of targeted LNCs



Significant enhancement of brain accumulation of OX26-LNC in rats

# Encapsulation of fluorescent dyes

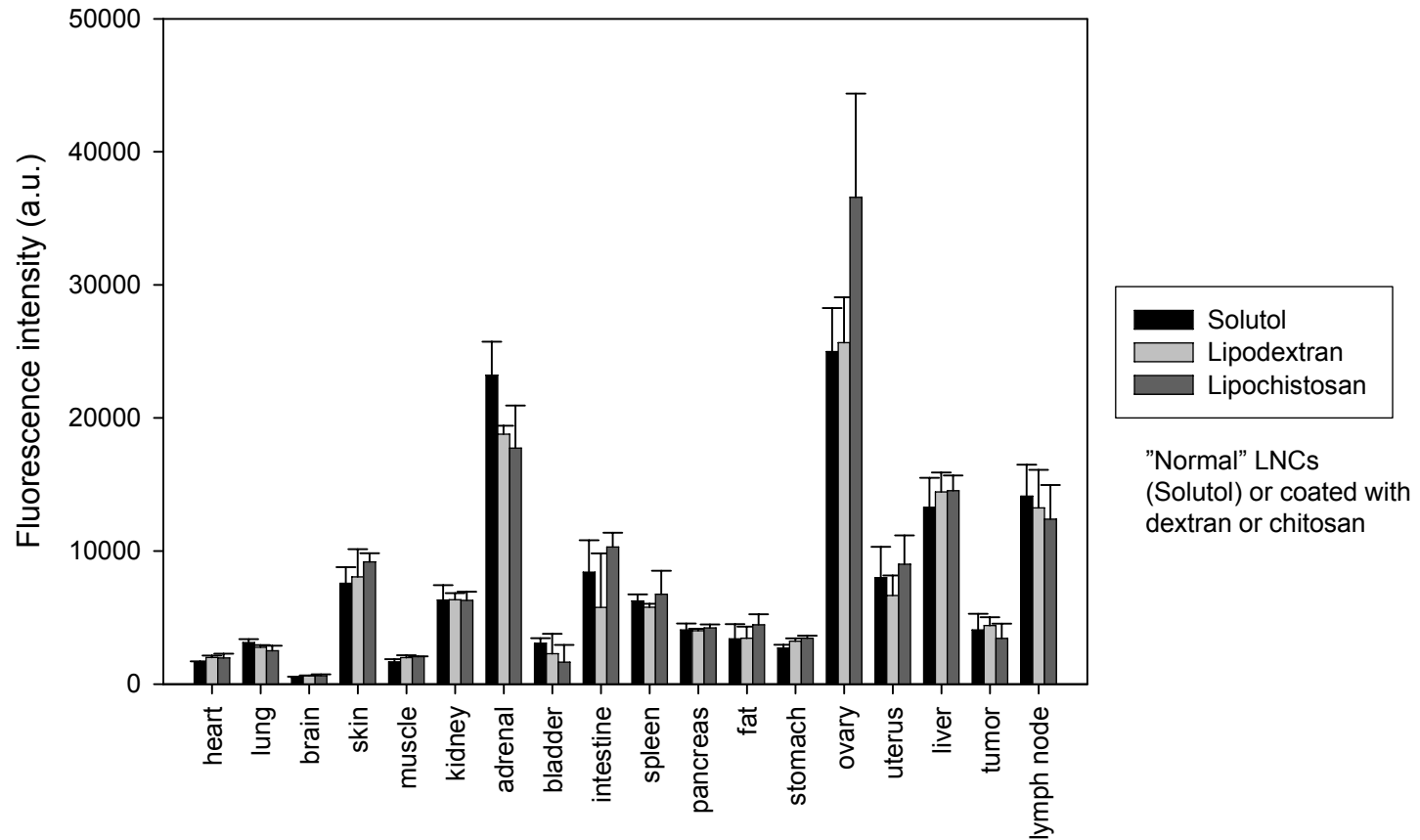
- Commercial hydrophobic indocyanines
  - DiD, DiO, DiR, Dil, ICG
- FRET pairs





# *In vivo* fate of LNC

LNC DiD 50nm, 24h after injection



# Project partners and funding

- **Inserm U646, Angers**
  - Samuli HIRSJÄRVI, Emmanuel GARCION Catherine PASSIRANI, Olivier THOMAS, Jean-Pierre BENOIT
- **DTBS CEA-LETI, Grenoble**
  - Julien GRAVIER, Isabelle TEXIER
- **Laboratoire Colloïdes et Matériaux Divisés, ESPCI, Paris**
  - Yan QIAO, Audrey ROYERE, Jérôme BIBETTE
- **Inserm U823, Grenoble**
  - Sandrine DUFORT, Jean-Luc COLL



- **Personal funding**
  - Academy of Finland, Alfred Kordelin Foundation, L'Association Franco-Finlandaise pour la Recherche Scientifique et Technique