





# Nanoparticle-based strategies in Oncology







INSERM 1066 - CNRS 6021  
**MiNT**

Prof. Jean-Pierre BENOIT

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## Innovating treatments in Oncology



Standard chemotherapy

Targeted therapies:


- Monoclonal antibodies
- Tyrosine kinase inhibitors



**Lymphoma**

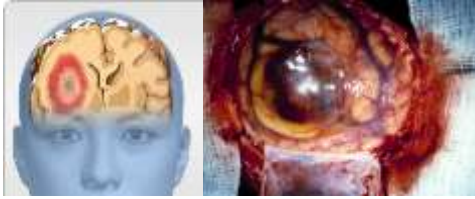
non-Hodgkin tumors

Gene therapy: CAR-T cells



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# Glioblastoma



- The most common primary brain tumor in adult
- After treatment, median survival <15 months
- Infiltrating tumor

Surgery  
Tumor removal

Stupp's protocol

Relapse

Evolution of the tumor after treatment

Recurrence in the 2 cms of the resection cavity (90%)

Temozolomide

Stupp R, *et al*, Lancet Oncol., 2009

## Design and development of intracerebral microparticulate implants

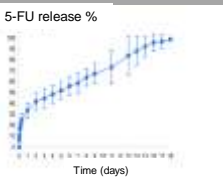
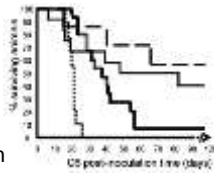
From bench...

Radiosensitization of malignant glioma  
5-FU Microspheres

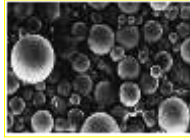
...to bedside



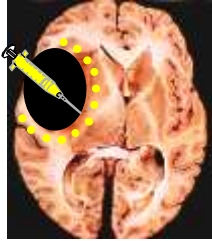
50-60µm



## Phase I/II and IIb clinical trials



5-FU PLGA Microspheres



### Phase IIb clinical trial

- 77 patients, 2 arms with or without MS
- No observed toxicity
- No recurrence at the vicinity of the tumor
- Significant prolongation of the median survival
- But need to extend the phase IIb to 200 patients or more to continue the development!

PLGA= Poly(lactide-co-glycolide)

Menei, *et al*, *Cancer*, 1999; *Cancer*, 2004; *Neurosurgery*, 2005, 56(2), 242

## Nanomedicine : Nanotechnologies applied to Medicine

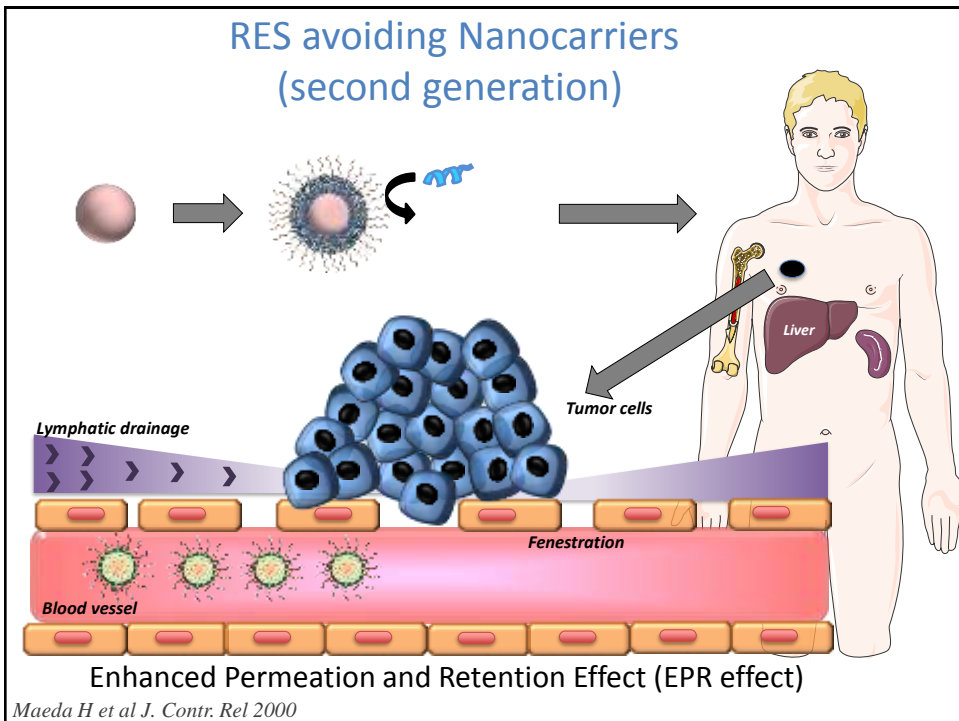
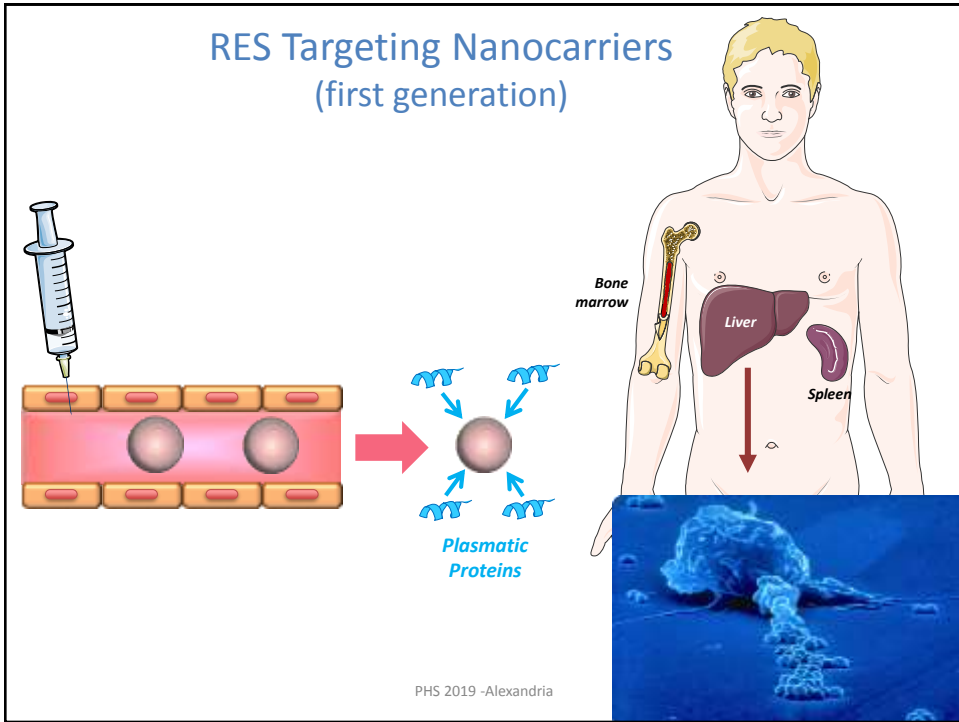
1 nm =  $10^{-9}$  m = one billionth meter!

1 nm/1 m = Hazelnut/Earth

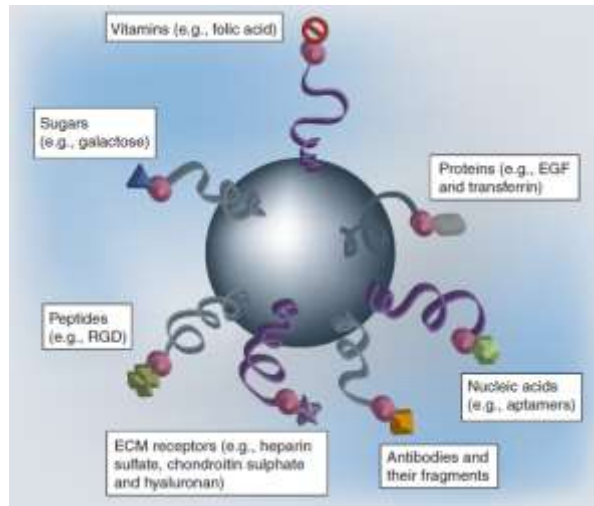
→ New properties



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## Third generation of nanocarriers: decorated nanocarriers with ligands



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## EPR-positive tumors

Stealth nanosystems will work nicely

Hureau J., *et al*, Pharm Res, 2010; Hirsjärvi S, *et al*, Nanomedicine, 2013...

## EPR-negative tumors

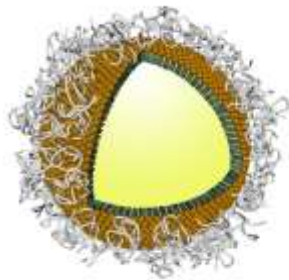
- New nanomedicines, new strategies and new routes of administration to induce new antitumoral activity profile
  - **Chemotherapy**
  - Radiotherapy

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## Lipid Nanocapsules (LNC)



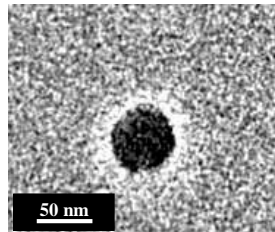
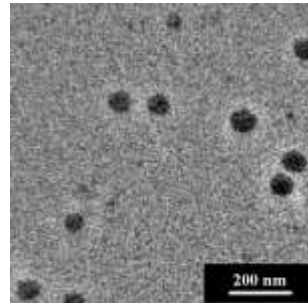
- ▣ Biomimetic System: to mimic the structure of a lipoprotein
- 4  $\varnothing < 100\text{nm}$ , monodisperse and stable
- 4 Only FDA-approved excipients



Oil

Phospholipid

Pegylated surfactant

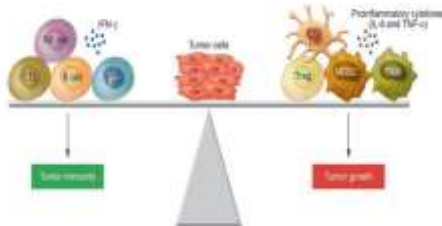


(Heurtault B, et al, Pharm. Res., 2002)

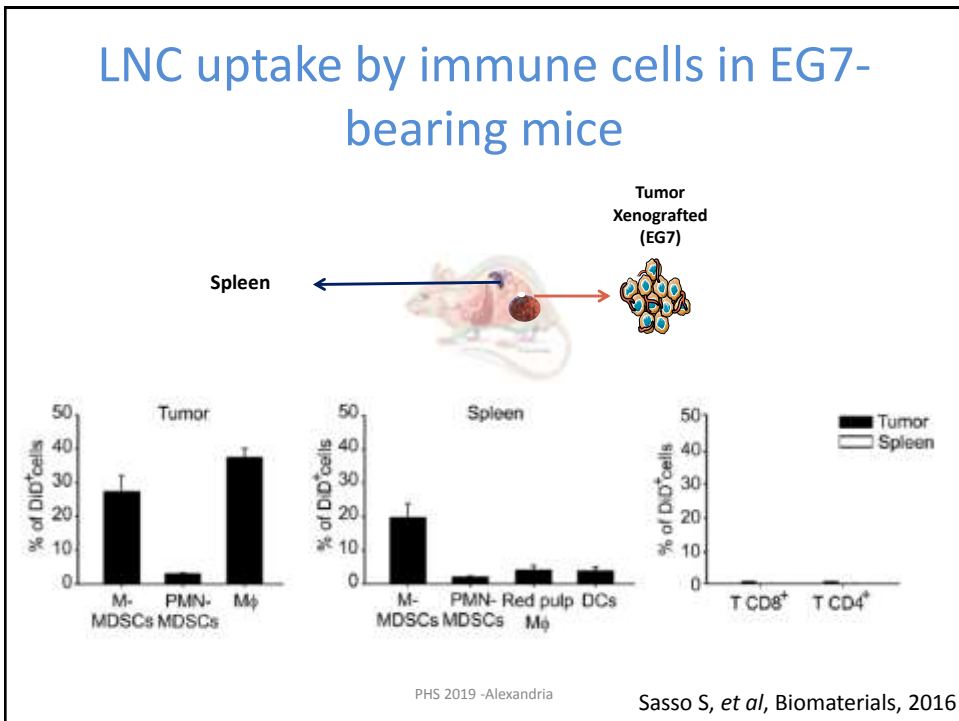
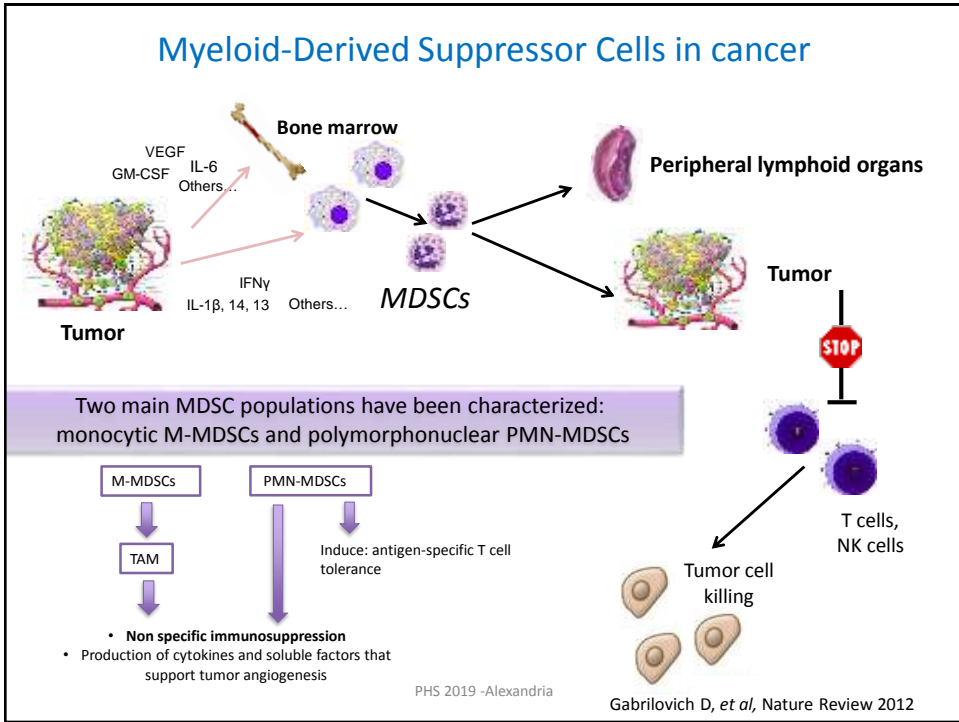
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## Cancer immunology and immunotherapy. Realizing the promise

According to the National Cancer Institute definition, immunotherapy is any ‘treatment to boost or restore the ability of the immune system to fight cancer, infections, and other diseases’

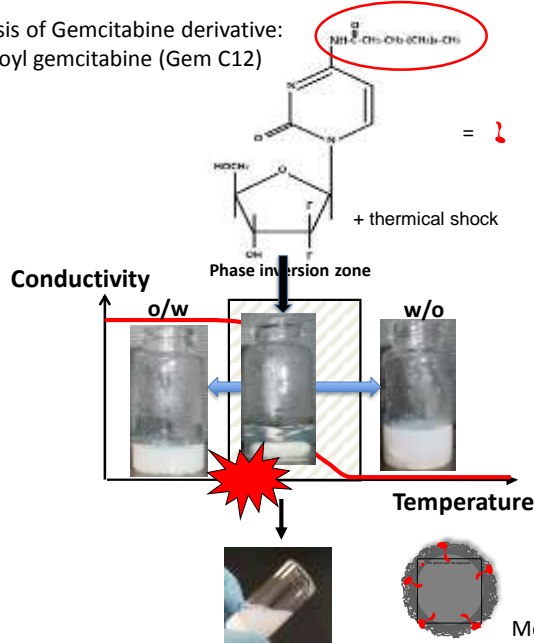


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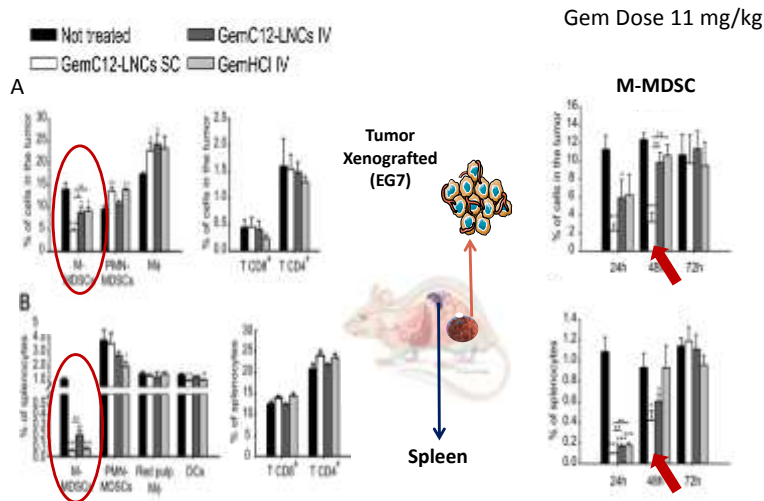


## GemC12-loaded lipid nanocapsules (GemC12-LNC)

→ Synthesis of Gemcitabine derivative:  
4-(N)-lauroyl gemcitabine (Gem C12)



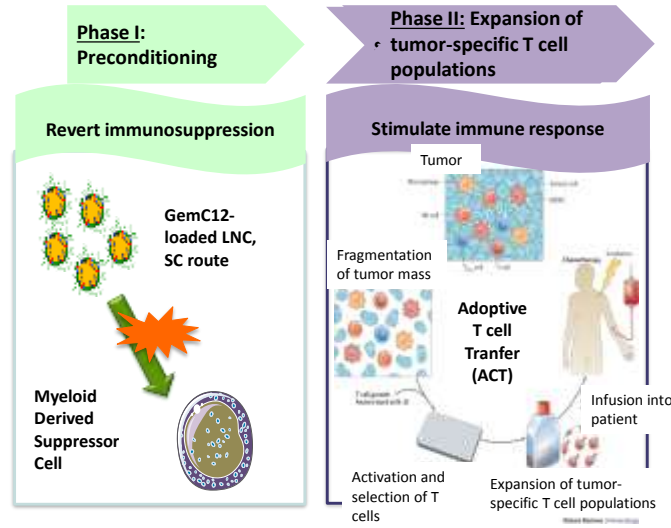
## Reduction of M-MDSC by GemC12-LNC



SC injection of GemC12-LNC (11 mg/kg) enhanced M-MDSC reduction as compared with IV injection

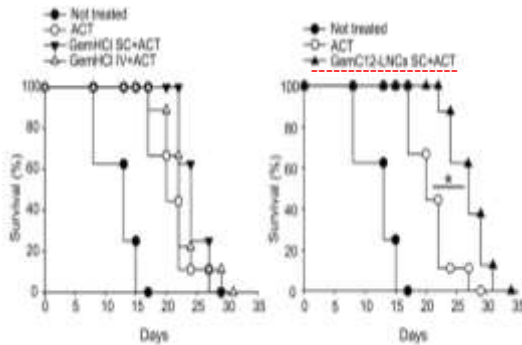
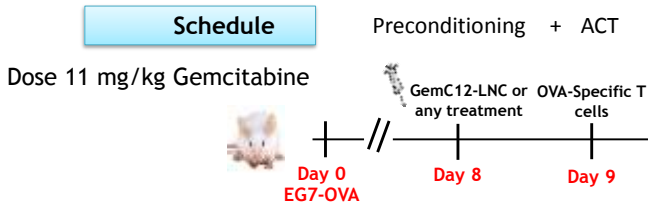


# In vivo Antitumor activity: the effect of a combined therapy



Restifo, *et al*, Nature Reviews Immunology, 2012

## Antitumor activity of Gem-C12 LNC combined with ACT: EG7-OVA tumor



Preconditioning with low dose of GemC12-LNC, SC infused, enhances Adoptive T Cell Transfer (ACT) efficacy

Sasso S, *et al*, Biomaterials, 2016

## EPR-positive tumors

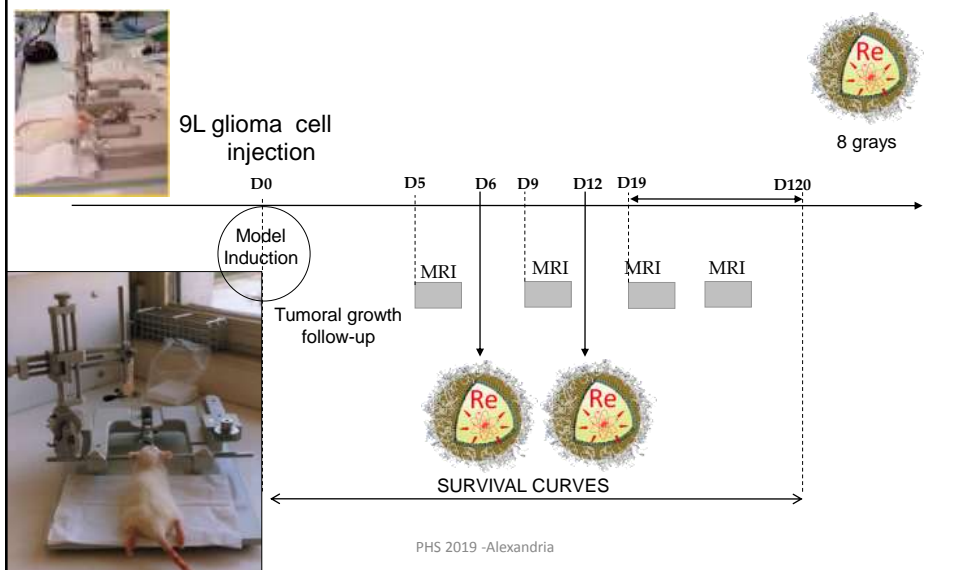
Stealth nanosystems will work nicely

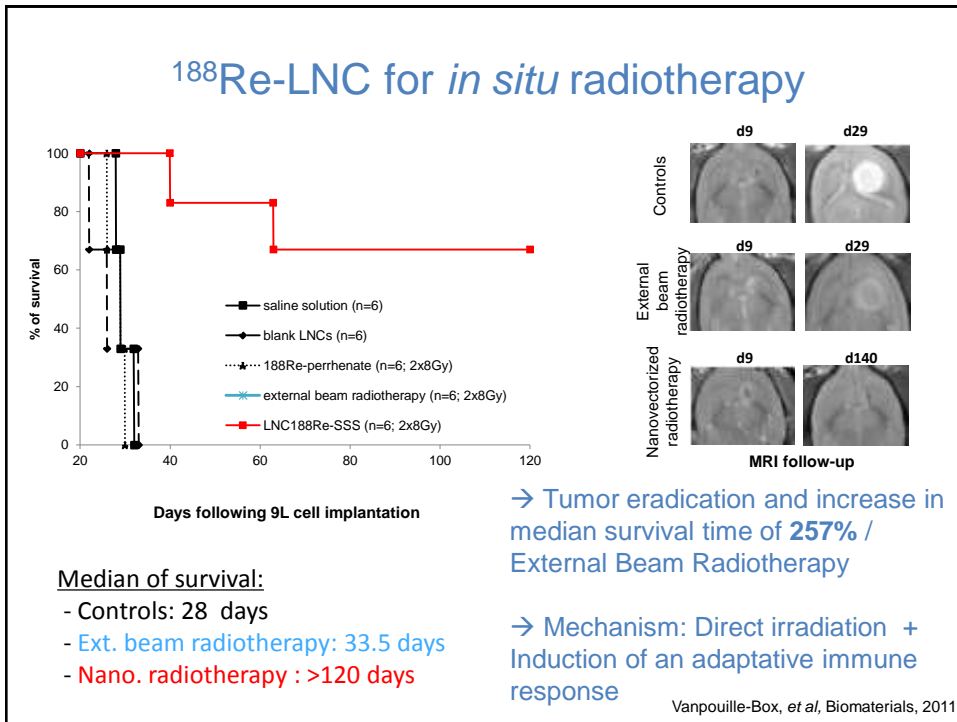
## EPR-negative tumors

- New nanomedicines, new strategies and new routes of administration to induce new antitumoral activity profile
  - Chemotherapy
  - **Radiotherapy**

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## $^{188}\text{Re}$ -LNC for *in situ* radiotherapy Local administration





## Conclusion: contribution of nanomedicines to Oncology

- EPR-positive tumors: +++ if stealth nanosystems
- EPR-negative tumors:
  - Design of nanocarriers having new properties (i.e. interaction with specific immune subsets,...)
  - Exploring other routes of administration to reveal new biodistribution profiles
  - Setting new paradigms: nano-immunotherapy, *in situ* radiotherapy,...

Marie-Claire Venier, Guillaume Bastiat, Elodie Moysan, Marion Pitorre, Claire Vanpouille

In collaboration with Prof V. Bronte (Univ.Verona), Dr G. Lollo (Univ. Lyon)









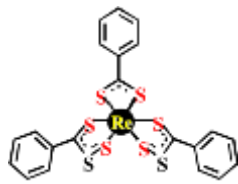
LYMPHOTARG, NICHE, GLIOGEL      CALIF      EQUIPE LABELLISEE

### Radioactive LNC for *in situ* radiotherapy

**Rhenium-188**

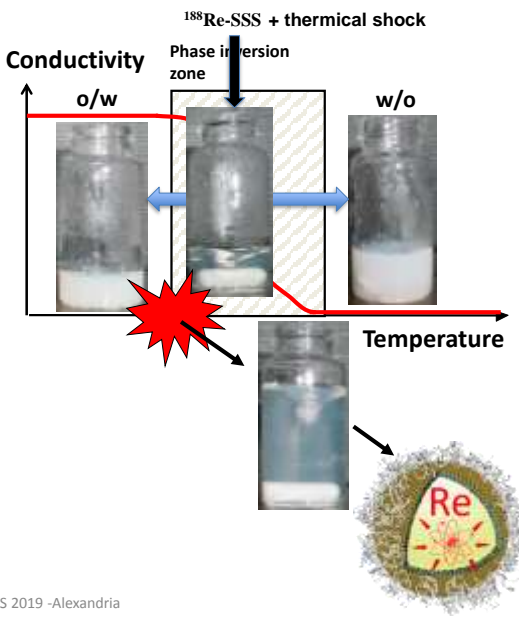
- $^{188}\text{W}/^{188}\text{Re}$  generator
- High  $\beta^-$  energy (2,12 MeV)
- Low  $\gamma$  emission (155 keV)
- Short half-life (17h)

↓



**$^{188}\text{Re-SSS}$**

*Collaboration : Pr. N Noiret, Pr. E Garin (Rennes)  
Mévellec, et al, Inorg Chem. 2002*



$^{188}\text{Re-SSS}$  + thermal shock

Conductivity ↑

Phase inversion zone

o/w      w/o

Temperature →

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