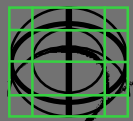


APPORT DES NANOTECHNOLOGIES DANS LA CONCEPTION DE NOUVEAUX MEDICAMENTS: APPLICATION AU CANCER

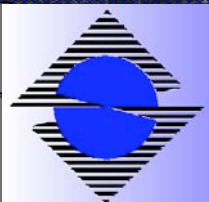
P. COUVREUR

UMR CNRS 8612, Université Paris-Sud

Colloque du Centre d'Alembert, 10 Mai 2006

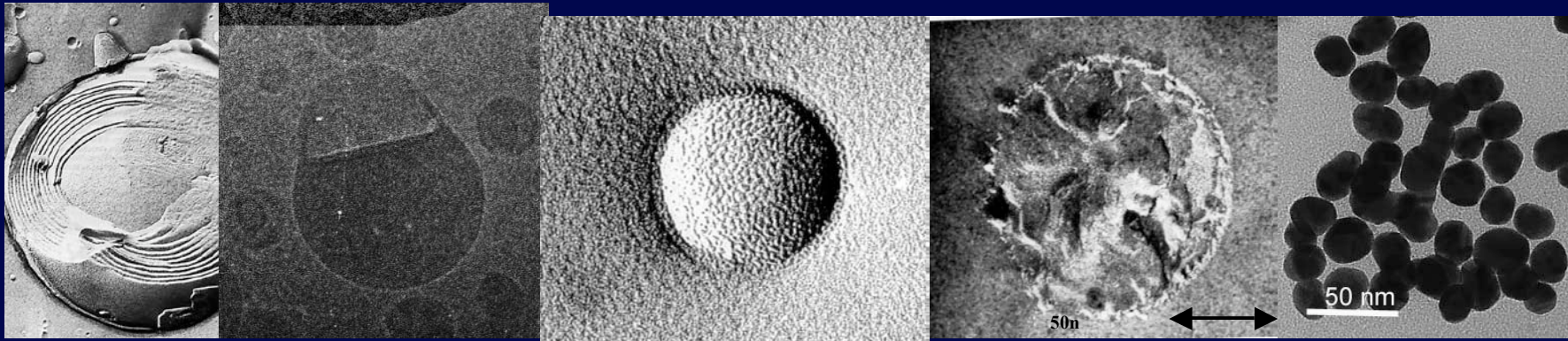


UMR CNRS 8612



DIVERSITE DES NANOOBJETS DE PREMIERE GENERATION POUR LA VECTORISATION DES MEDICAMENTS

50 nm

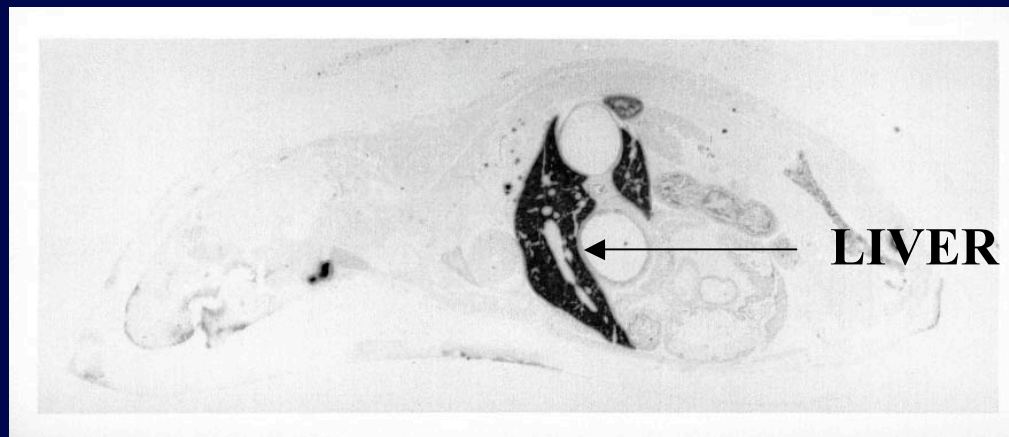


Liposome « Janus » vesicle

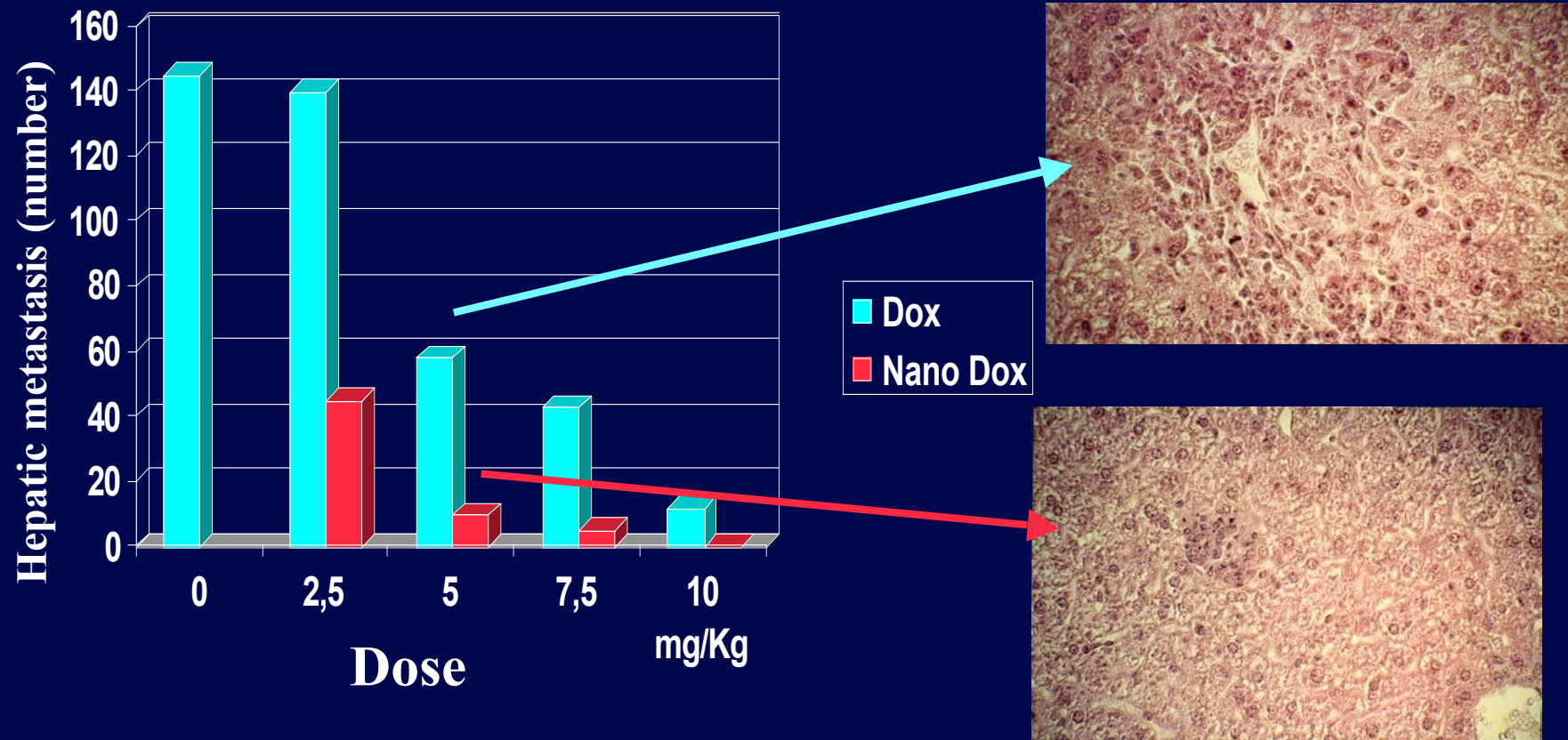
nanosphere

nanocapsule

USPIO

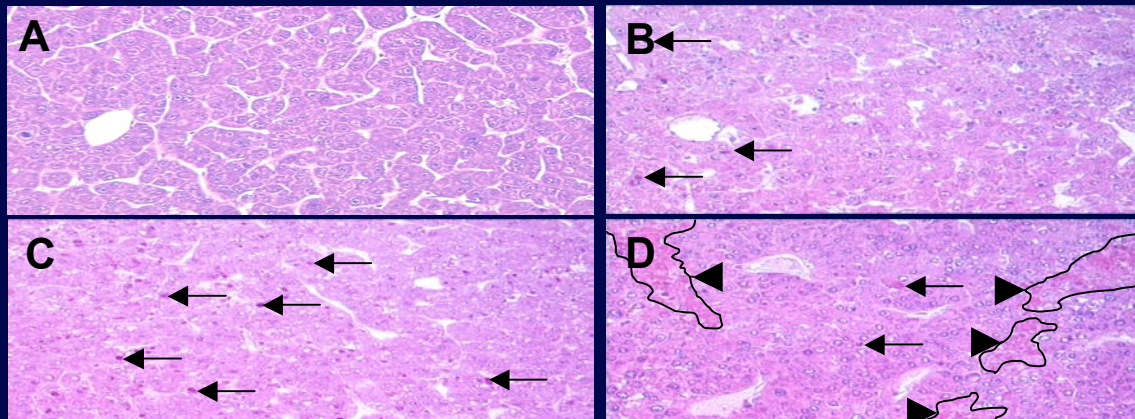
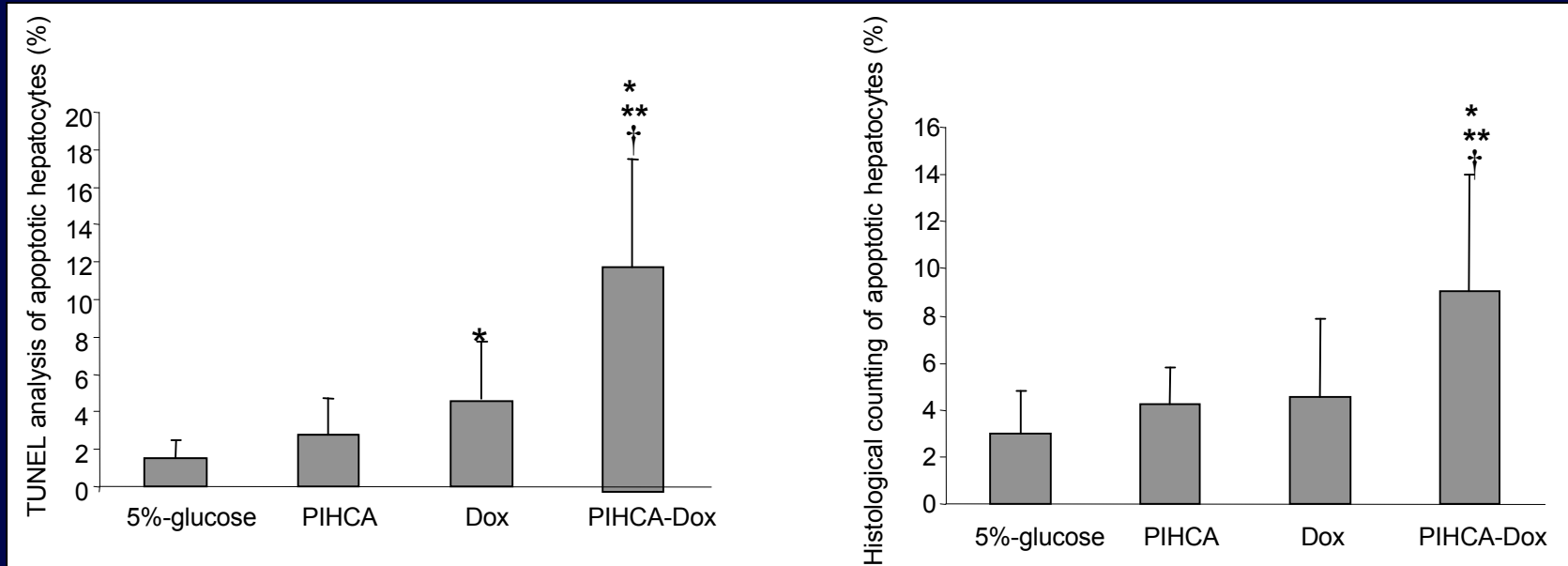


EFFICACITE ANTICANCEREUSE DE LA DOXORUBICINE VECTORISEE PAR DES NANOPARTICULES (Métastases hépatiques M5076)



N. Chiannikulchai, N. Ammouy, B. Caillou, JP Devissaguet, P. Couvreur, Cancer Chemother Pharmacol, 1990
N. Chiannikulchai, Z. Driouich, JP. Benoit, AL Parodi, P. Couvreur, Sel. Cancer Ther., 1989

EFFICACITE DE NANOPARTICULES CHARGEES EN DOXORUBICINE SUR UN MODELE EXPERIMENTAL DE SOURIS TRANSGENIQUES DEVELOPPANT UN HEPATOCARCINOME MDR RESISTANT



Arrows = apoptotic bodies in HCC tumors

- A. Colin de Verdière, C. Dubernet, F. Némati, E. Soma, M. Appel, J. Ferté, S. Bernard, F. Puisieux, P. Couvreur, *Brit. J. Cancer*, **76**, 198-205 (1997).

- L Barraud, P. Merle, E. Soma, L. Lefrançois, S. Guerret, Dubernet, P. Couvreur, C. Trépo, *J. Hepathol*, **42**, 736-743 (2005)

ESSAIS CLINIQUES (Bioalliance)

✓ HCC Phase I/II :

Response ⁺	#
Partielle	*8
Absence de réponses	5
Complète	**3
Total Patients	16

⁺ As of 16 June 2005

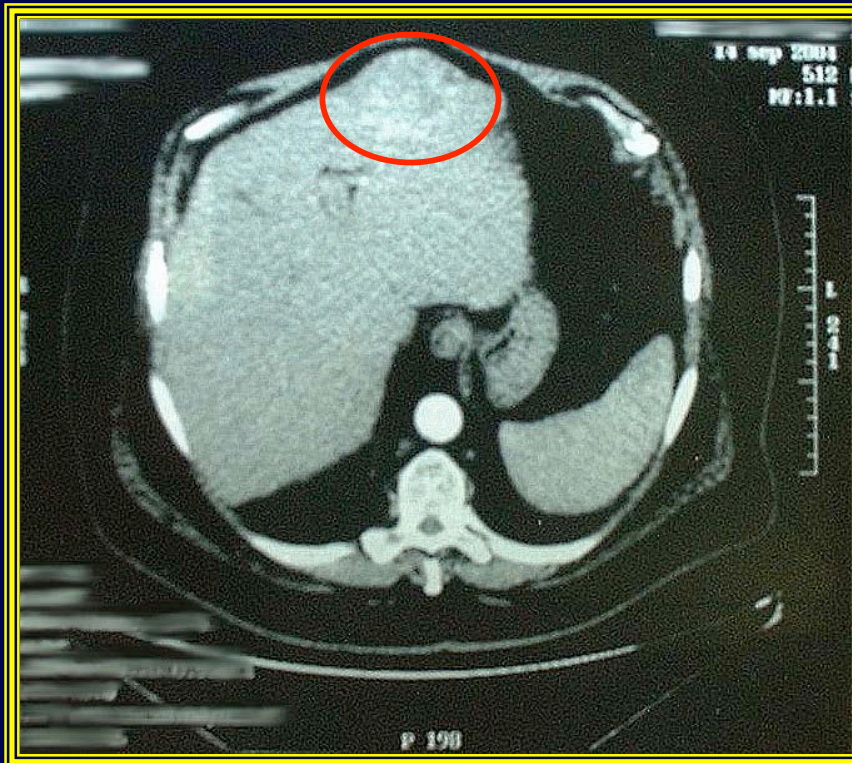
* Includes 1 patient with 2 completed cycles (patient number 13)

** Includes 1 patient with 2 completed cycles (patient number 8)

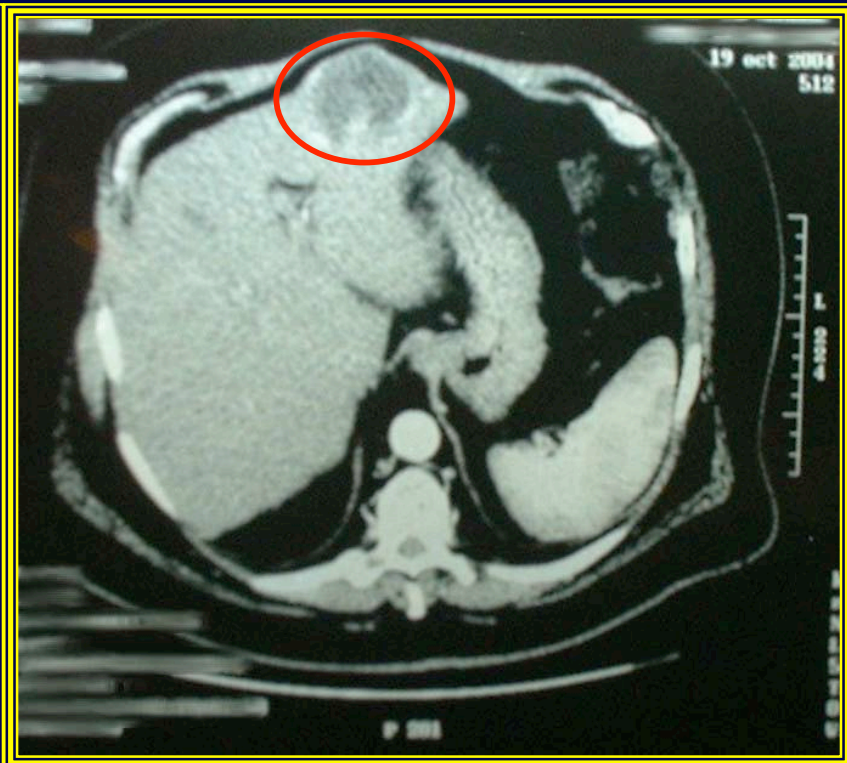
® ESSAI CLINIQUE (Bioalliance)

Patient #8: Présentant une simple tumeur non résécable du Segment II
Taille de la tumeur: 60 x 50 mm (3000mm²)

1 x 30 mg/m², la nécrose tumorale est évidente



Avant traitement



**4 semaines après traitement:
nécrose tumorale évidente**

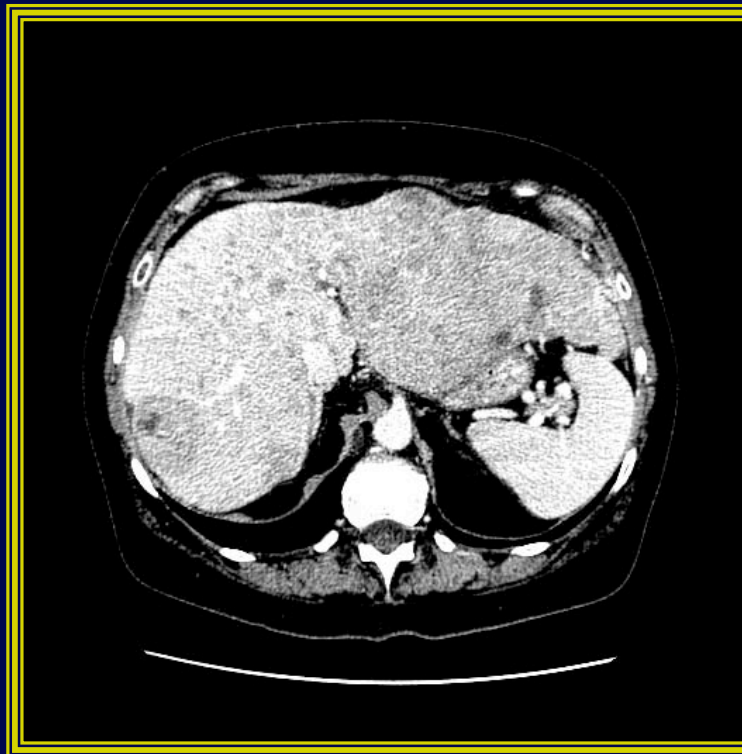
® ESSAIS CLINIQUES (Bioalliance)

Patient #16: Présentant une pathologie tumorale disséminée

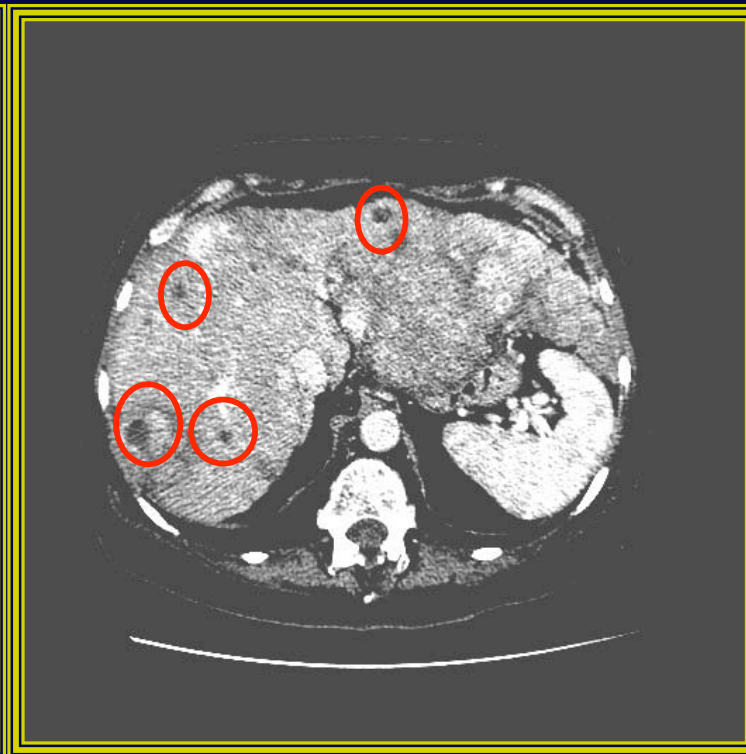
1 x 35 mg/m², nécrose tumorale accompagnée d'une réduction significative du taux d'alpha-fœto protéine

AFP: 268,900 microG/L

AFP: 103,800 microG/L

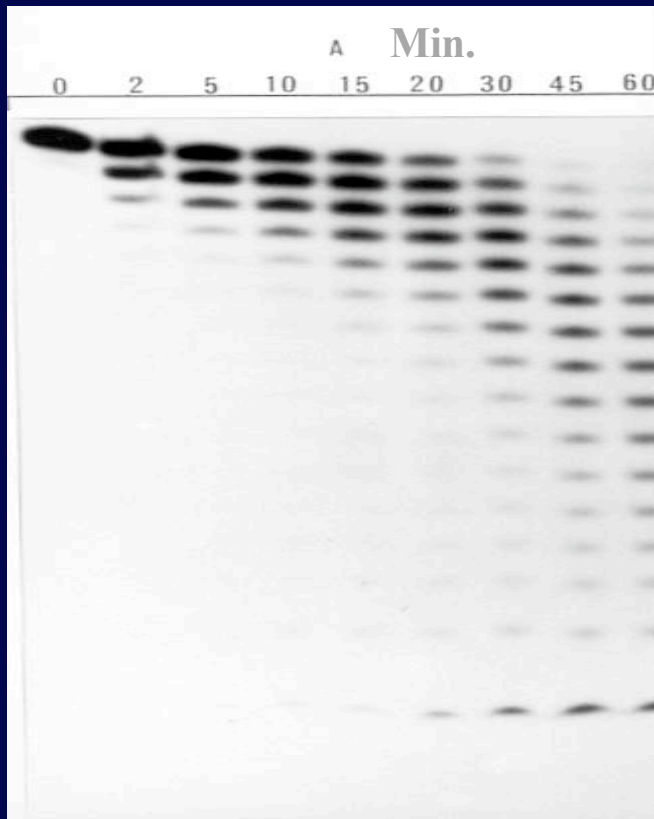


Avant traitement

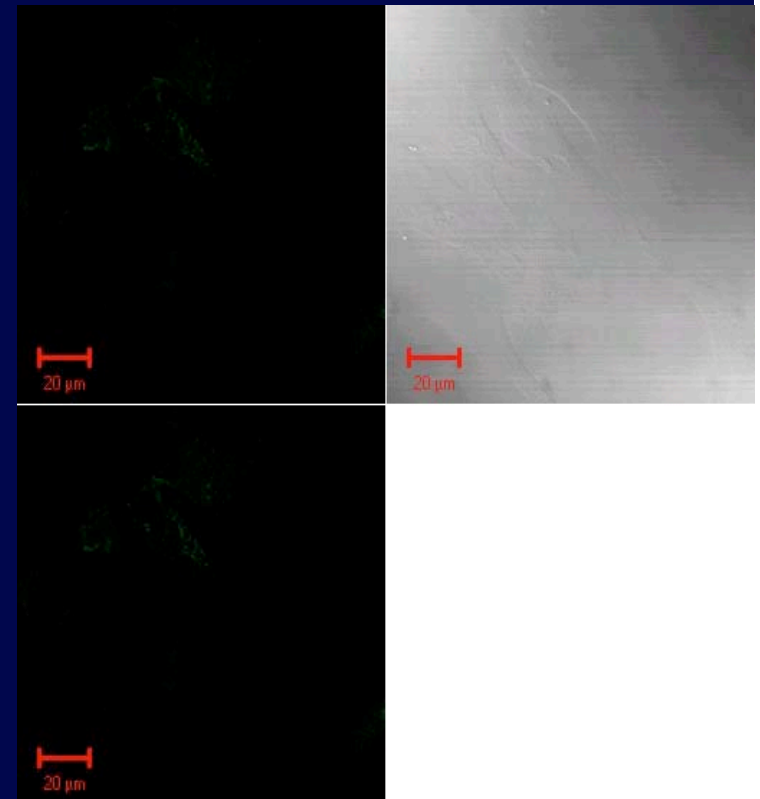


**4 semaines après le
traitement: nécrose tumorale
évidente**

COMMENT ADMINISTRER L'INADMINISTRABLE ?

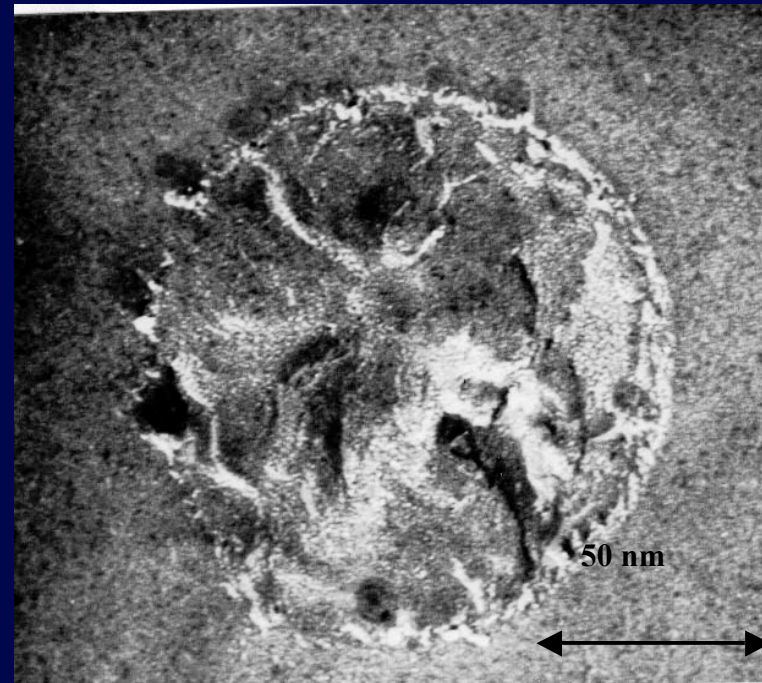
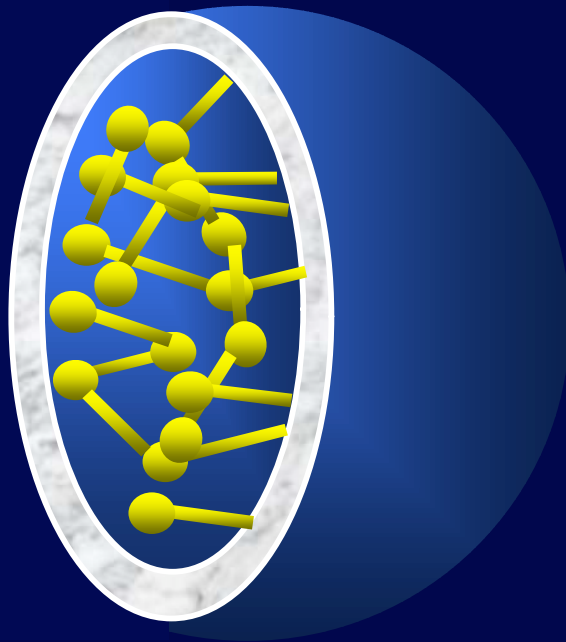


Degradation of ODN
In calf serum (10%)



Intracellular penetration

NANOCAPSULES A CONTENU AQUEUX POUR L'ADMINISTRATION DE COURTS FRAGMENTS D'ACIDES NUCLEIQUES (siRNA ou oligonucléotides)



G. Lambert, E. Fattal, H. Pinto-Alphandary, A. Gulik, P. Couvreur, *Pharm. Research*, 2000

G. Lambert, E. Fattal, H. Pinto-Alphandary, A. Gulik, P. Couvreur, *Int. J. Pharm.*, 2001

G. Lambert, E. Fattal, P. Couvreur, *Advanced Drug Delivery Reviews*, 47, 99-112, 2001

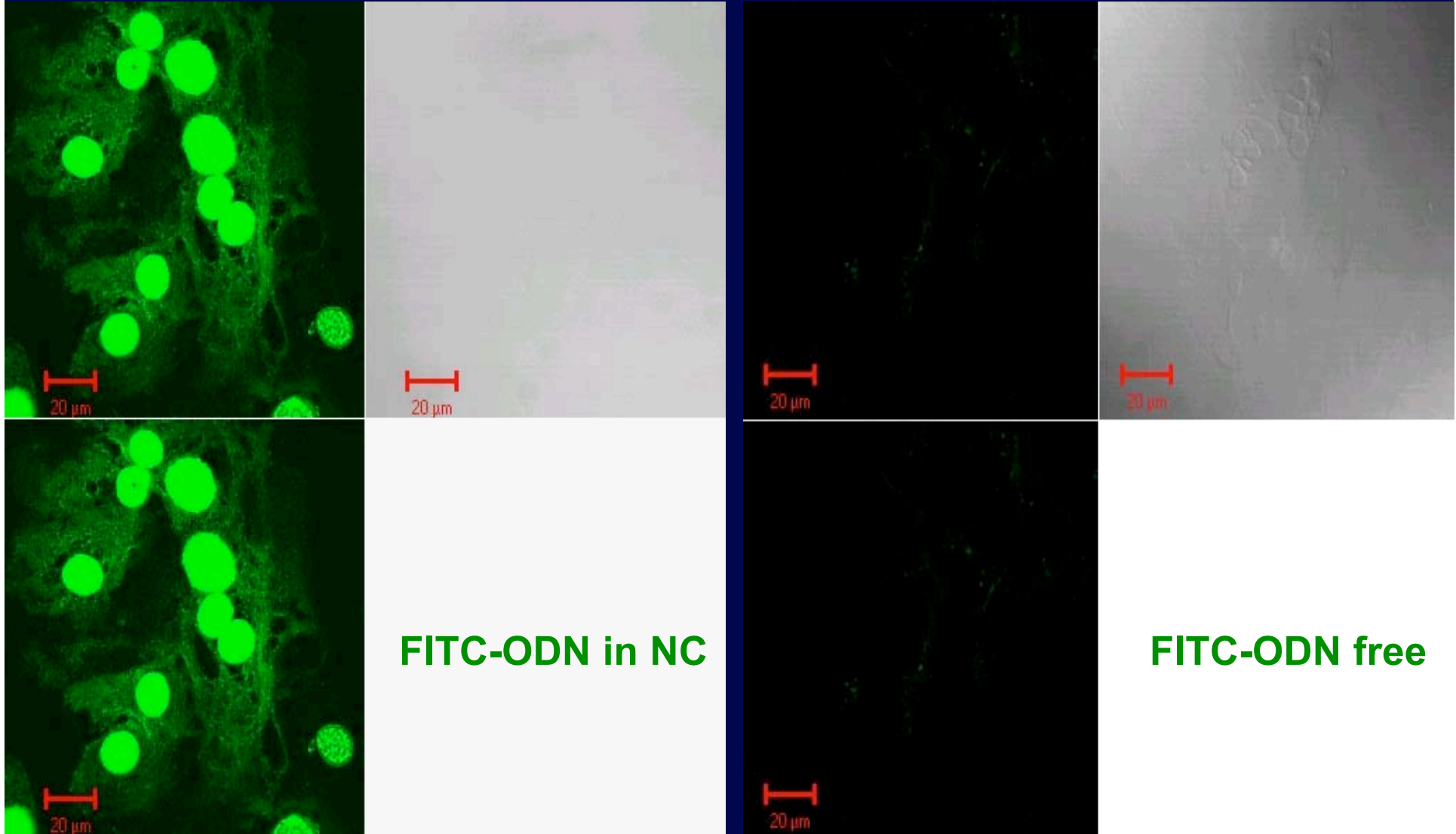
G. Lambert, J.R. Bertrand, E. Fattal, F. Subra, H. Pinto-Alphandary, C. Malvy, C. Auclair, P. Couvreur, *BBRC*, 2001

A. Maksimenko, C. Malvy, G. Lambert, J.R. Bertrand, E. Fattal, P. Couvreur, *Pharm. Research*, 2003

CAS DU SARCOME D'EWING

- **Translocation t(11 ; 22) (q24 ; q12)**
Chromosomique
Fli-1 = facteur de transcription (Chromosome 11)
EWS = activateur transcriptionnel (Chromosome 22)
- **EWS-Fli-1 = protéine chimère**
---> cancérisation

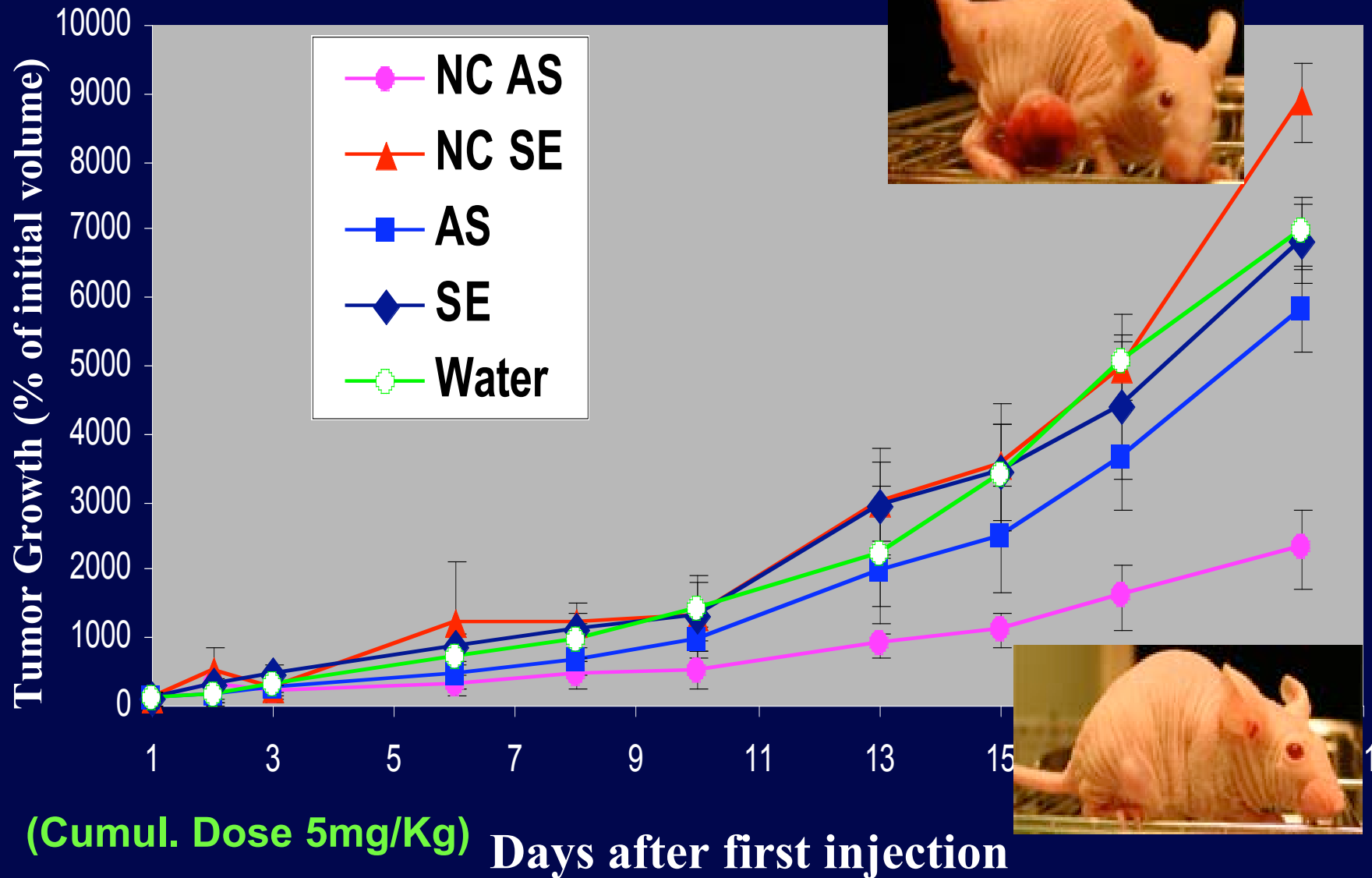
MICROSCOPIE CONFOCALE MONTRANT L'ENTREE DANS LA CELLULE DES ODNs VECTORISES PAR NANOCAPSULES



EFFICACITE DES NANOCAPSULES D'ODN SUR LE SARCOME D'EWING

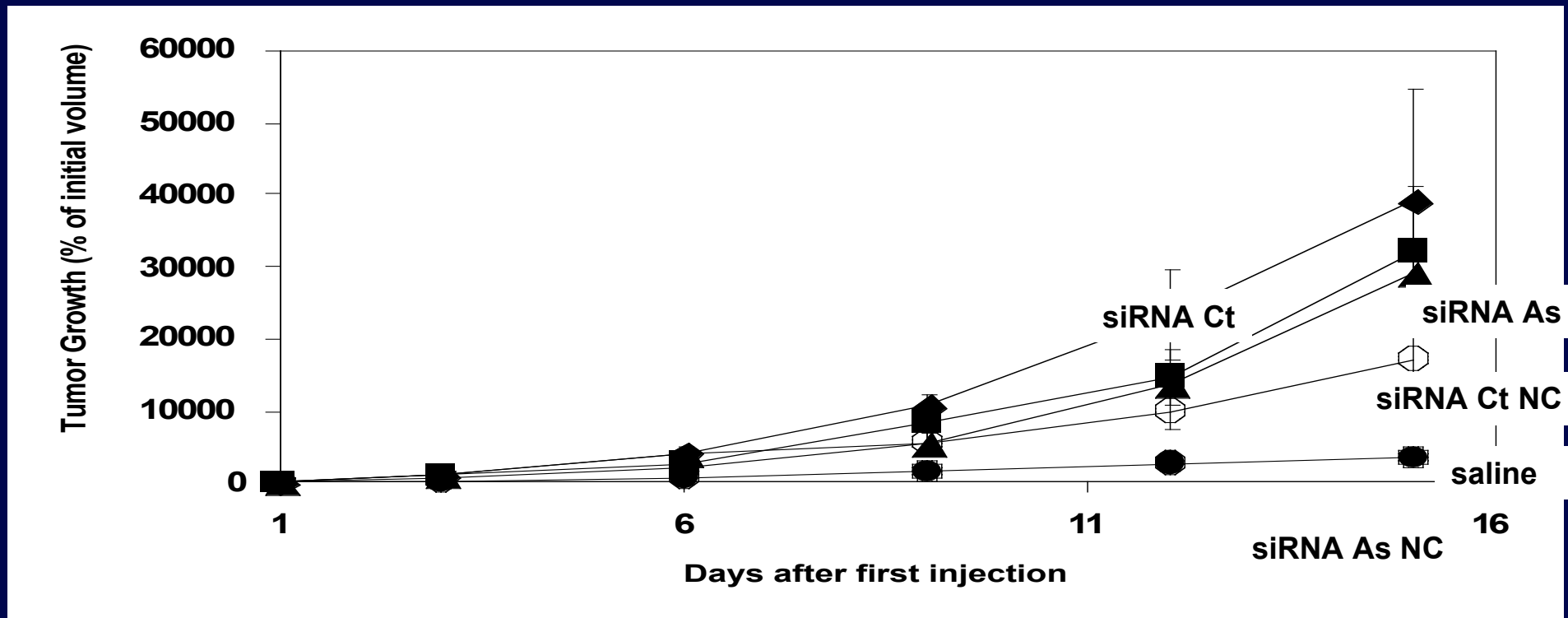
-G. Lambert, J.R. Bertrand, E. Fattal, F. Subra, H. Pinto-Alphandary, C. Malvy, C. Auclair, P. Couvreur, BBRC, 2001

- N. Toub, J-R Bertrand, A. Tamaddon, H. Elhamess, H. Hillaireau, A. Maksimenko, C. Malvy, E. Fattal and P. Couvreur, Pharm. Res, 2006



EFFICACITE ANTITUMORALE DE siRNA ENCAPSULES DANS LES NANOCAPSULES

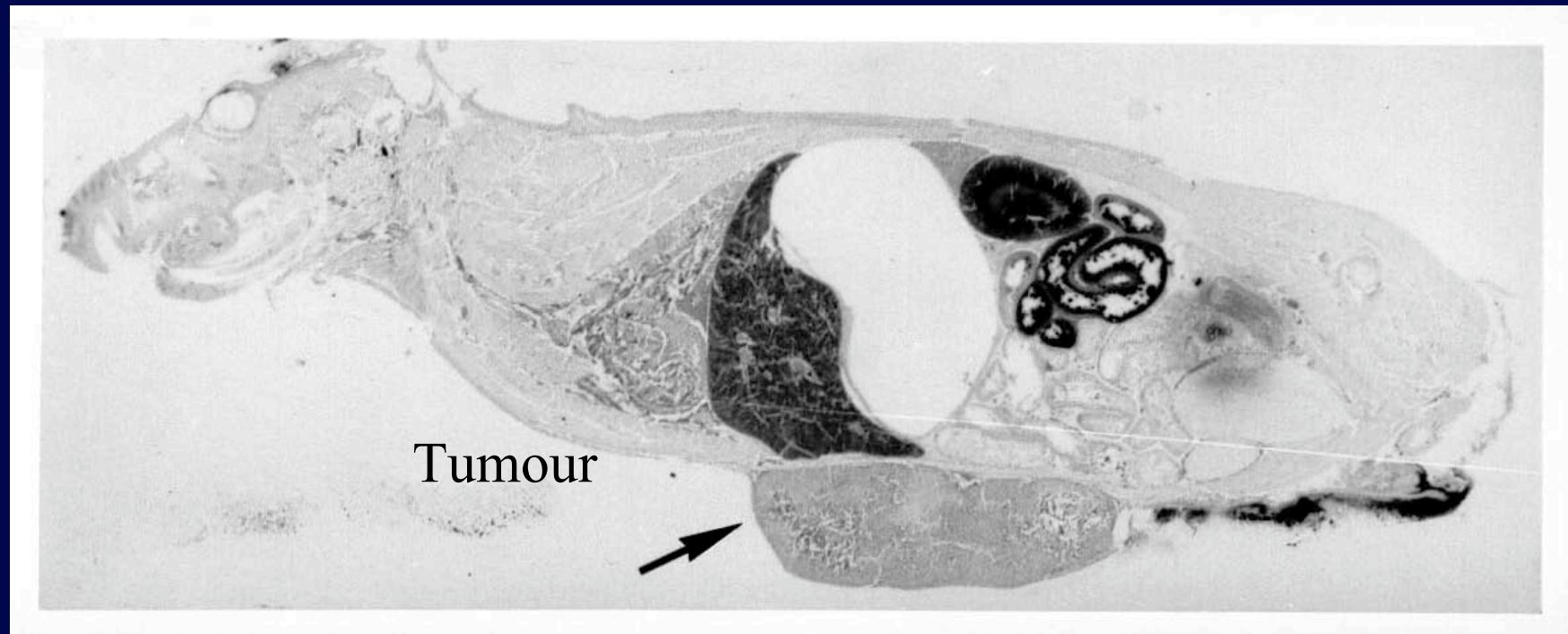
Dose: 5 injections 0.4 nM= 1.11 mg/kg



DEUXIEME GENERATION DE VECTEURS

LES NANOSYSTEMES
« FURTIFS »

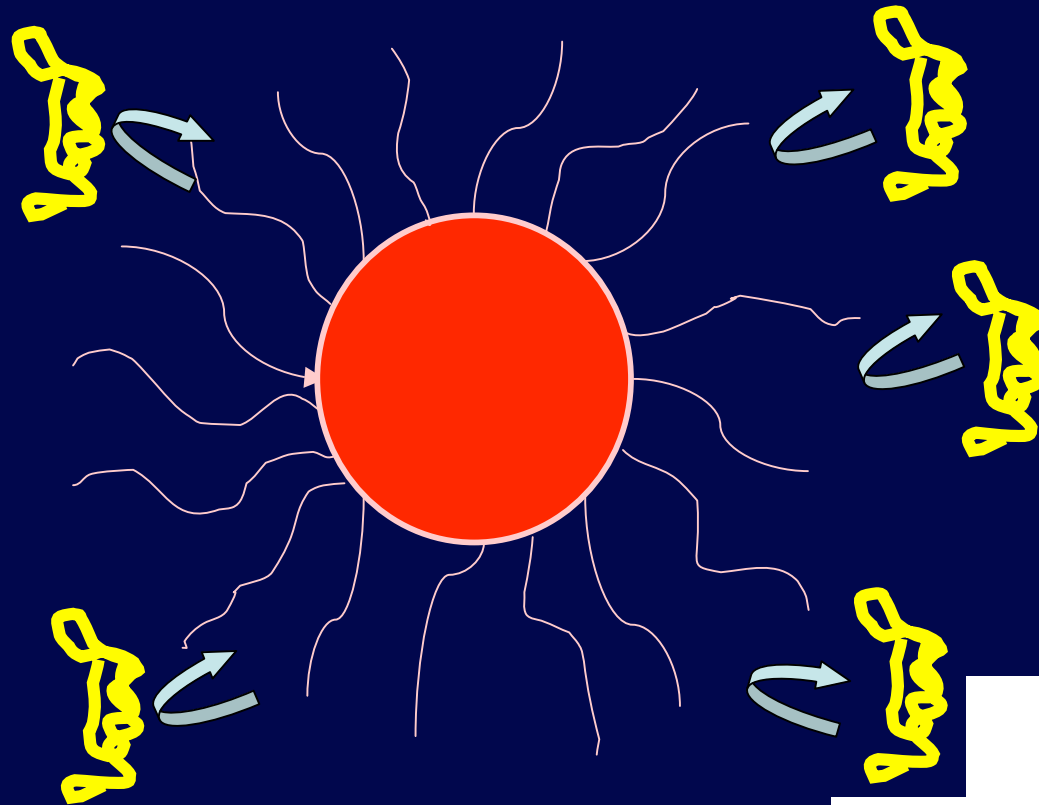
LES NANOOBJETS DE PREMIERE GENERATION ONT UN TROPISME HEPATIQUE



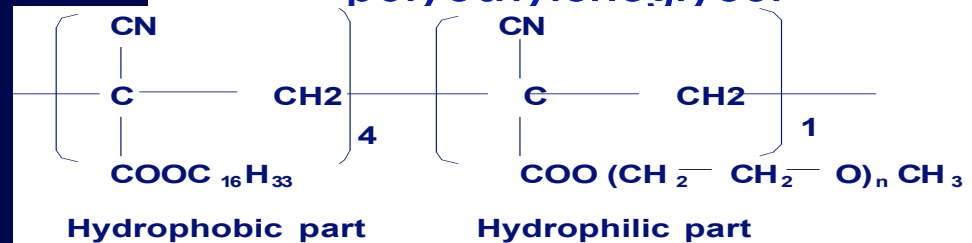
LES VECTEURS DE DEUXIEME GENERATION

M.T. Perrachia, D. Desma_le, P. Couvreur, J. d'Angelo,
Macromolecules, 30,846-851 (1997)

M.T. Peracchia, C. Vauthier, D. Desma_l, A. Gulik, M. Demoy,
J. D'Angelo, P. Couvreur, Pharm. Res., 15, 550-556 (1998)

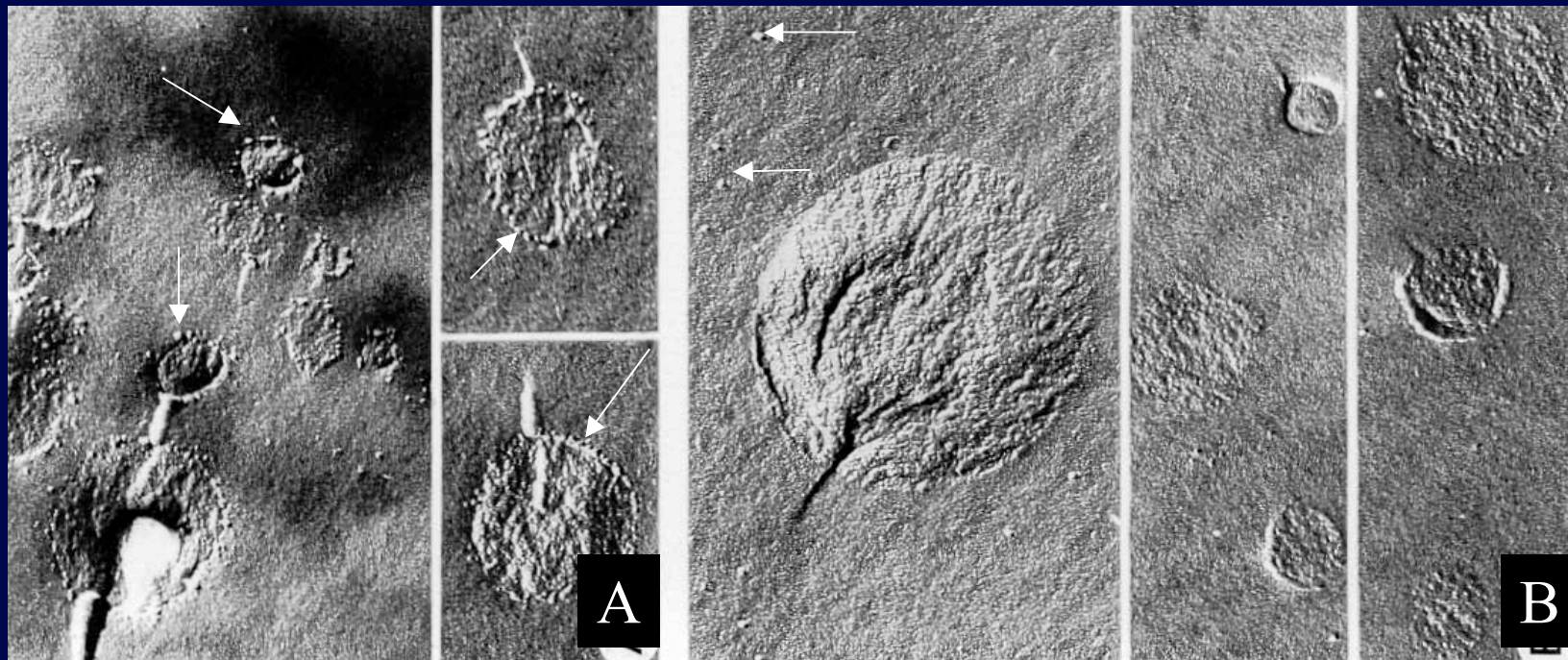


Polyhexadecyl-co-polyethyleneglycol



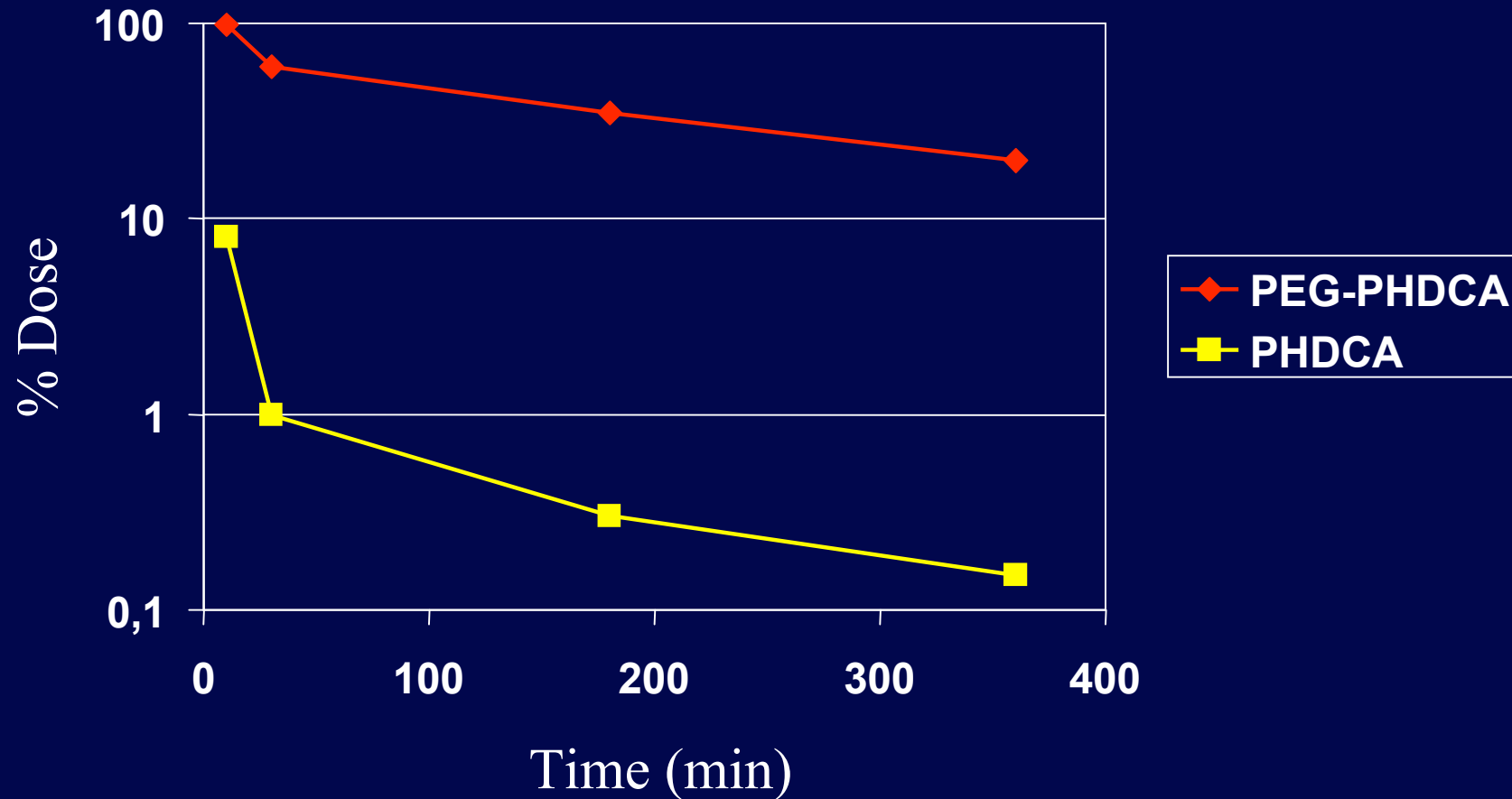
LES VECTEURS DE DEUXIEME GENERATION NE PERMETTENT PAS AUX PROTEINES DU SANG DE LES RECOUVRIR

(M-T Perracchia, S. Harnisch, H. Pinto-Alphandary, A. Gulik, JC. Dedieu,
D. Desmaël, J. D'Angelo, R. Muller, P. Couvreur, Biomaterials, 1999)

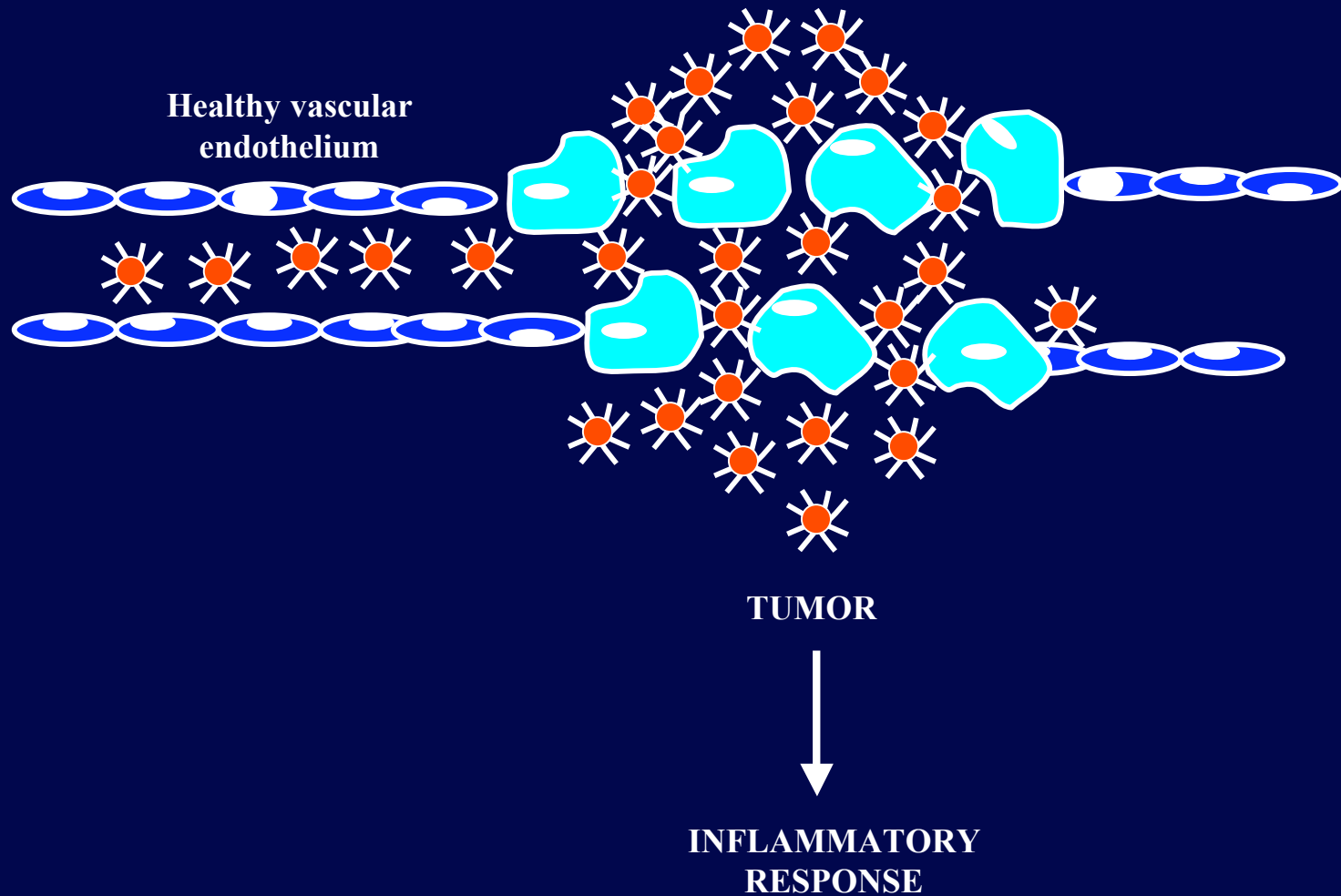


CONCENTRATION PLASMATIQUE DE NANOPARTICULES DE PREMIERE ET DE DEUXIEME GENERATION

(M-T. Perrachia, E. Fattal, M. Besnard, J-P.Noël, J-M. Gomis, M. Appel, J. d'Angélo, P. Couvreur, J. Control. Rel, 1999)

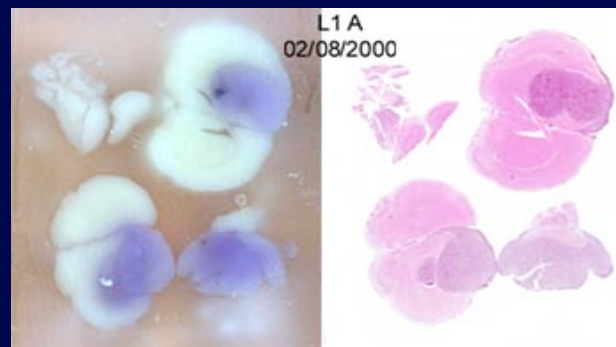
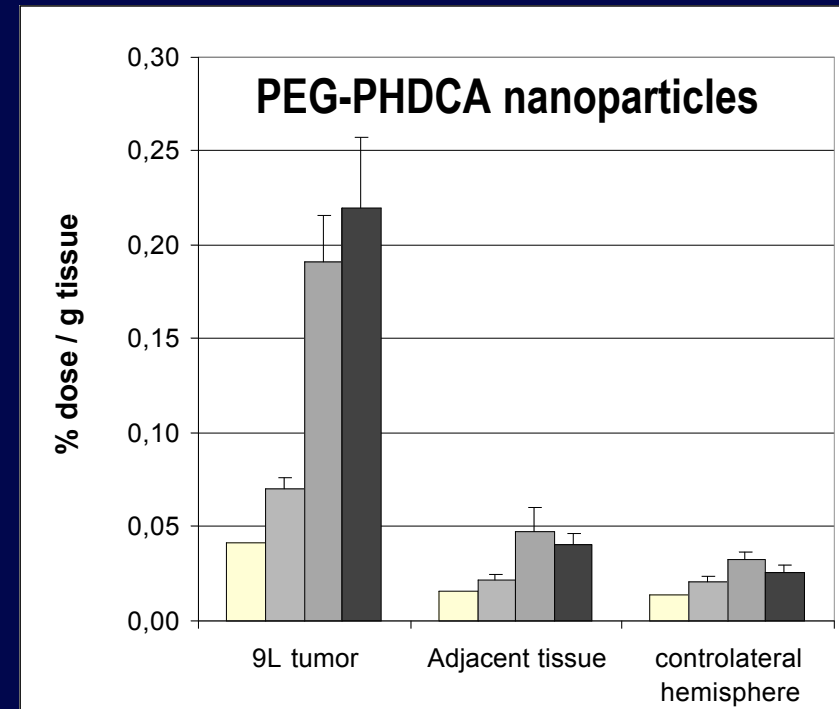
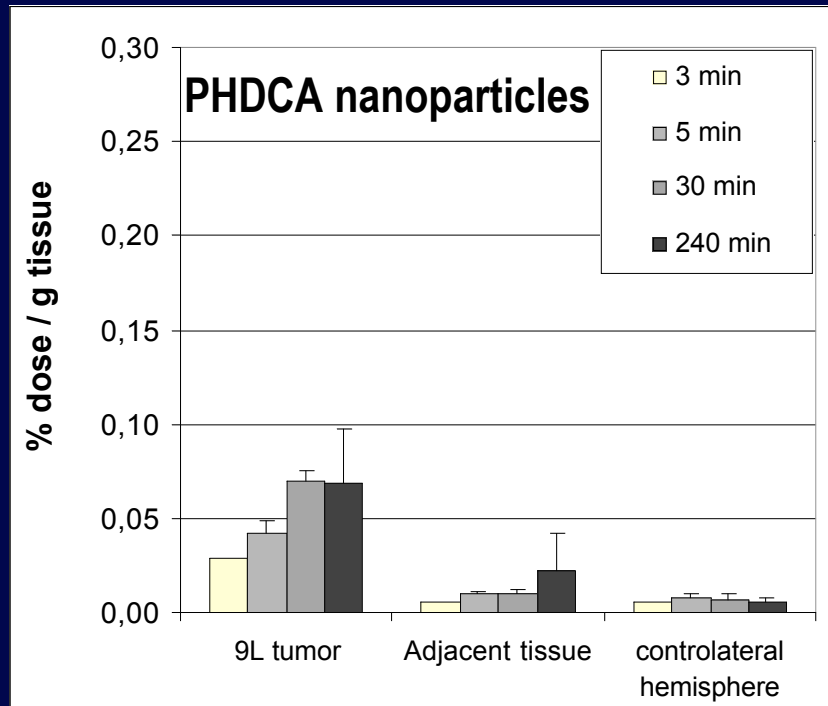


EXTRAVASATION TUMORALE SELECTIVE



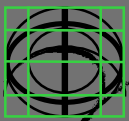
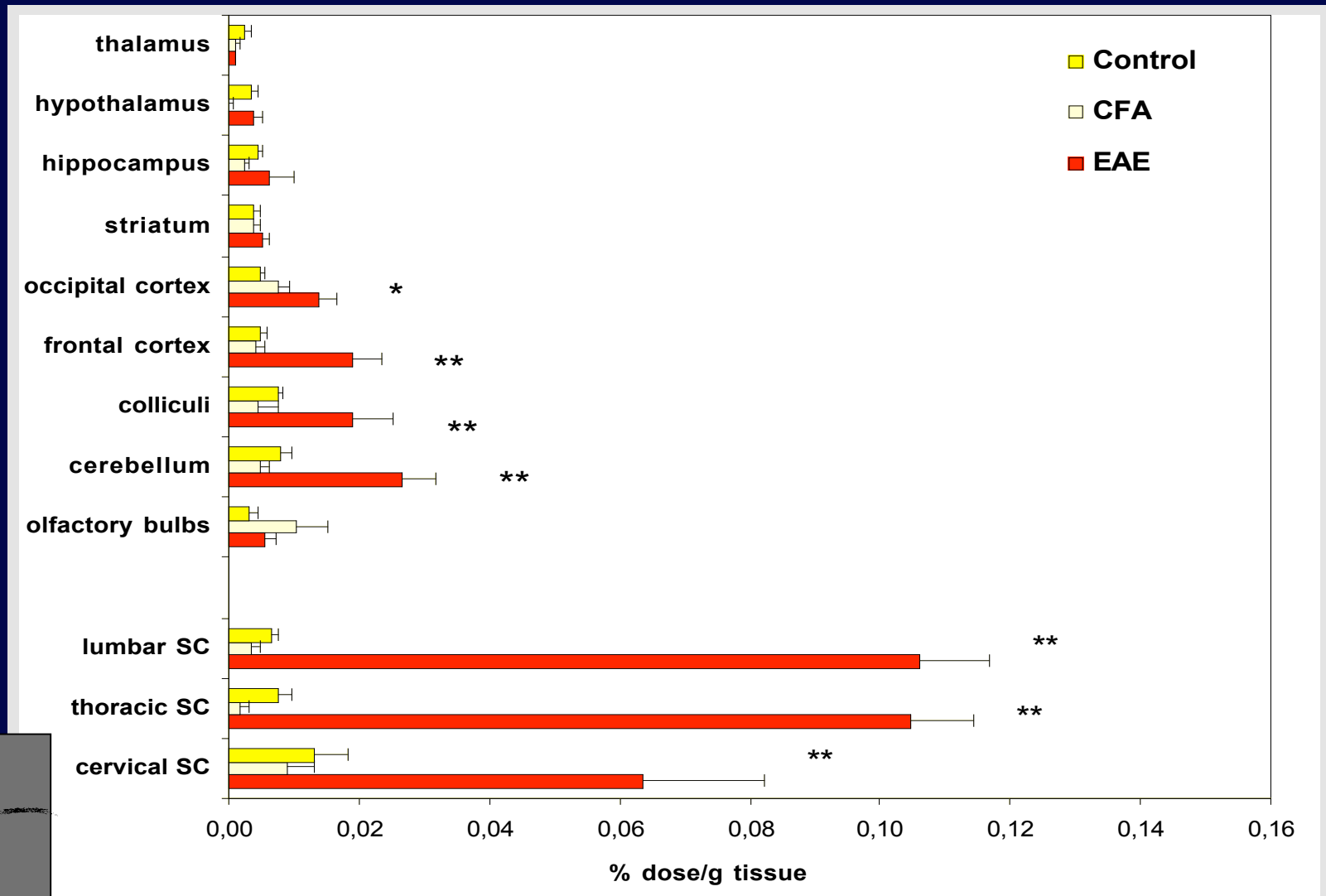
DISTRIBUTION INTRACEREBRALE DE NANOPARTICULES DE DEUXIEME GENERATION (GLIOSARCOME)

(I. Brigger, J. Morizet, G.Aubert, H. Chacun, M.-J. Terrier-Lacombe, P. Couvreur, G. Vassal, J. Pharmacol. Exp. Ther., 2002)



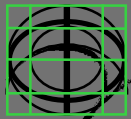
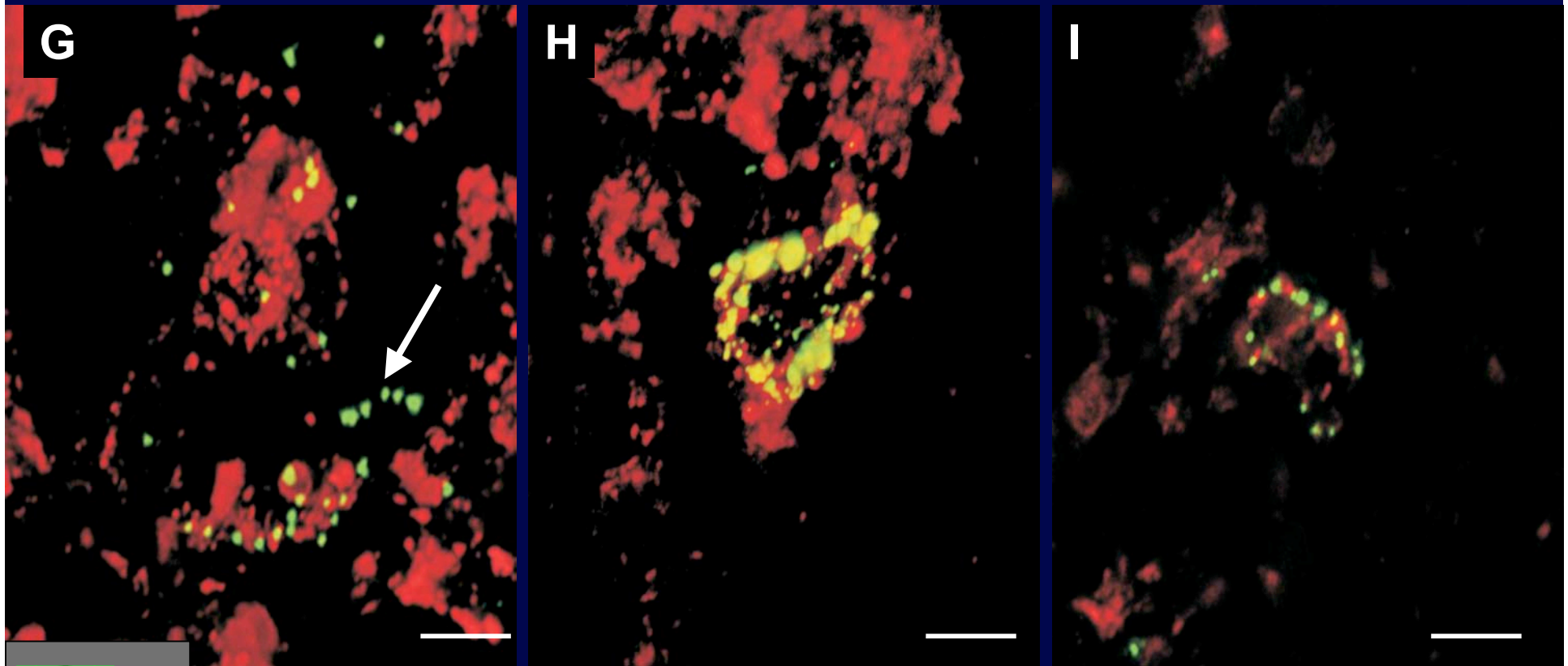
CAPTURE INTRACEREBRALE DES NANOPARTICULES ET ENCEPHALOMYELITE EXPERIMENTALE AUTOIMMUNE (EAE)

(P. Calvo, B. Gouritin, H. Villaroya, F. Eclancher, C. Giannavola, C. Klein, JP. Andreux, P. Couvreur, *Europ. J Neurosc.*, 15, 1317-1326, 2002)



MICROSCOPIE CONFOCALE DE COUPE TRANSVERSALE DE LA MOELLE EPINIERE D'ANIMAUX EAE MONTRANT LES NANOPARTICULES ET LES MACROPHAGES ED1+

(P. Calvo, B. Gouritin, H. Villaroya, F. Eclancher,
C. Giannavola, C. Klein, JP. Andreux, P. Couvreur,
Europ. J Neurosc., 15, 1317-1326, 2002)



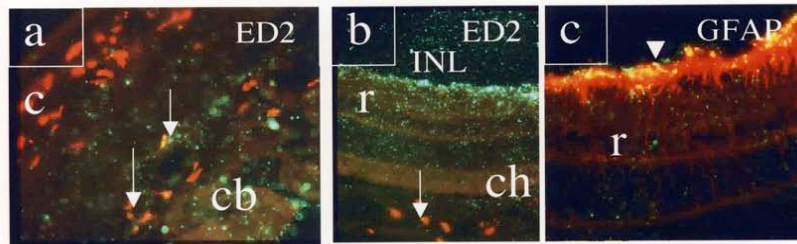
UVEITE EXPERIMENTALE AUTOIMMUNE (EAU)

- Mêmes caractéristiques physiopathologiques que l'EAE
- Mêmes modifications endothéliales dues au processus inflammatoires
- Le récepteur aux oestrogènes est impliqué dans la maladie, mais le tamoxifène est inefficace
- Absence de traitement

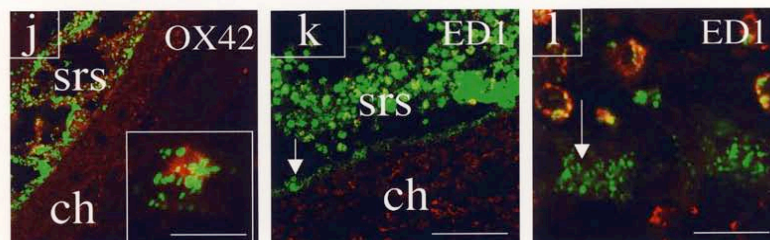
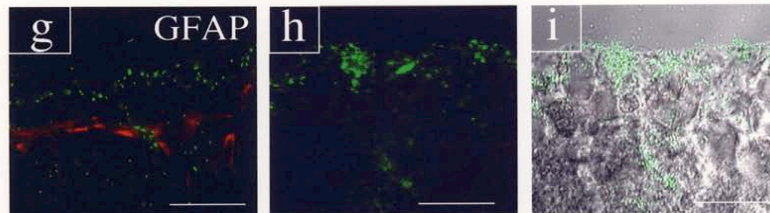
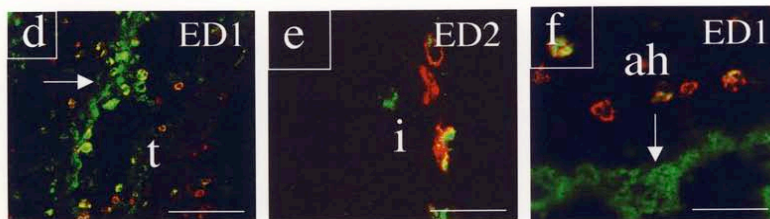
DISTRIBUTION INTRAOCULAIRE DES NANOPARTICLES DE PEG-PHDCA APRES ADMINISTRATION INTRAVITREALE A DES RATS SAINS OU PORTEURS DE L'UVEITE AUTOIMMUNE (EAU)

(Y. de Kozak, K. Andrieux, H. Villarroya, C. Klein, B. Thillaye-Goldenberg, MC. Naud, E. Garcia, P. Couvreur, *Europ J Immunol.*, 2004)

Non immunized controls



EAU

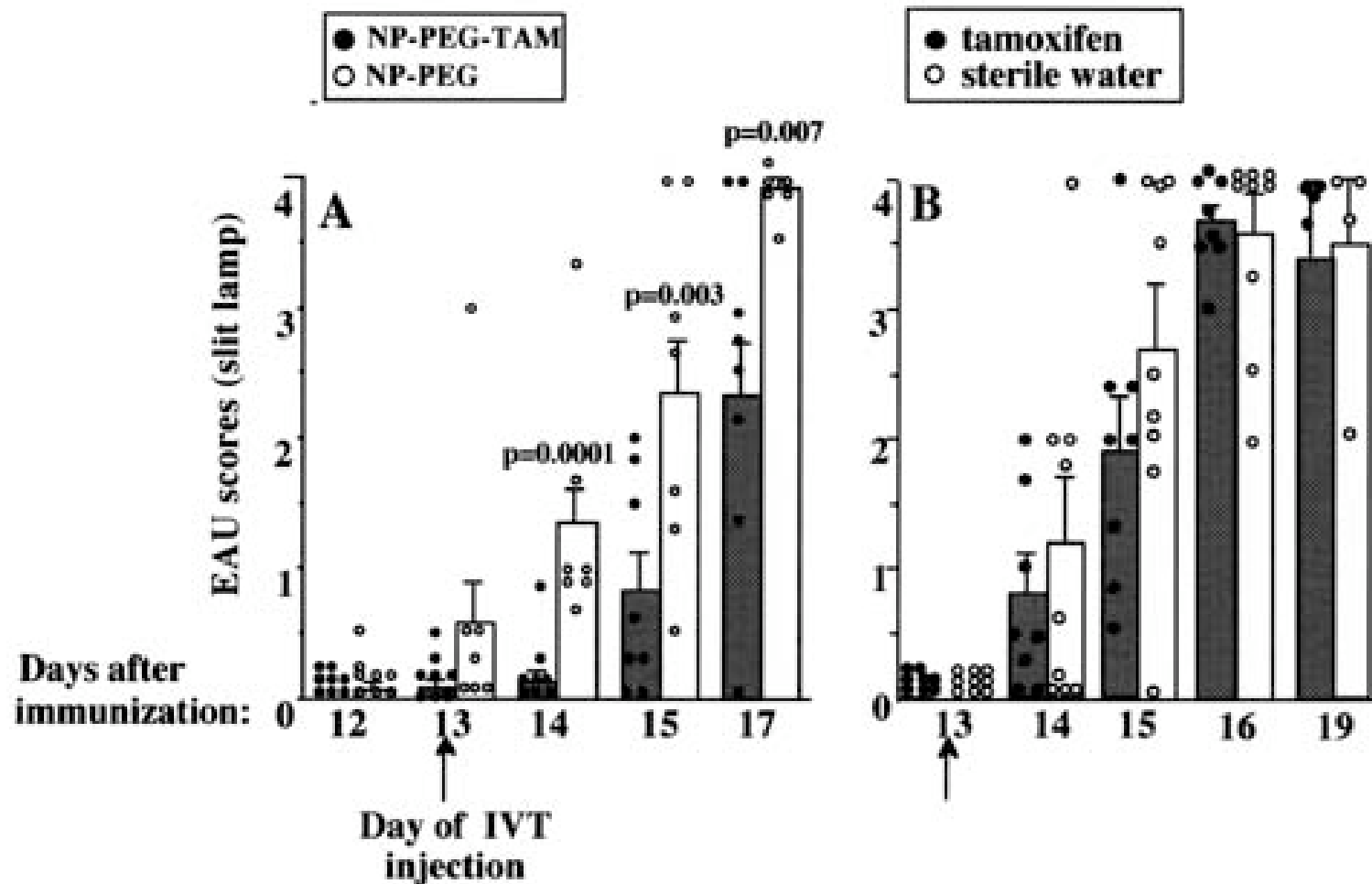


c corn_e
t trabeculum
i iris
r r_tine
ch choroid
cb corps ciliaire
ah humeur aqueuse

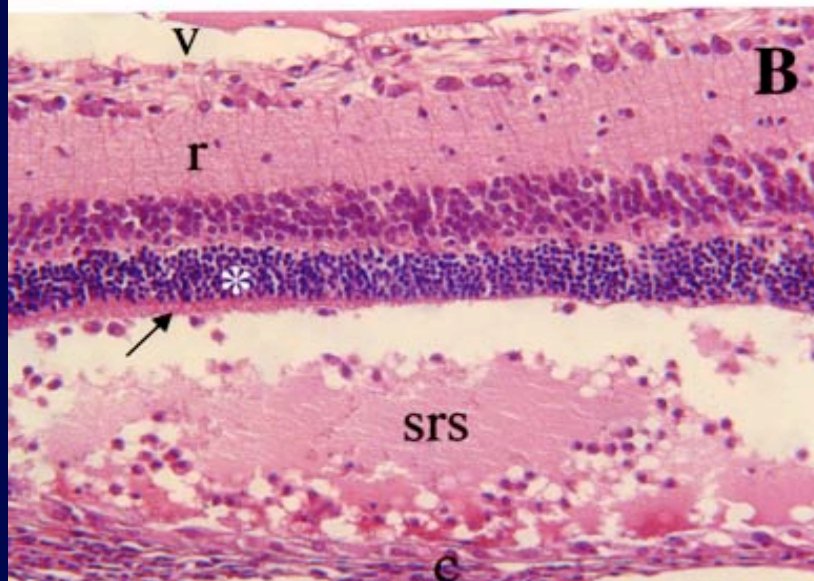
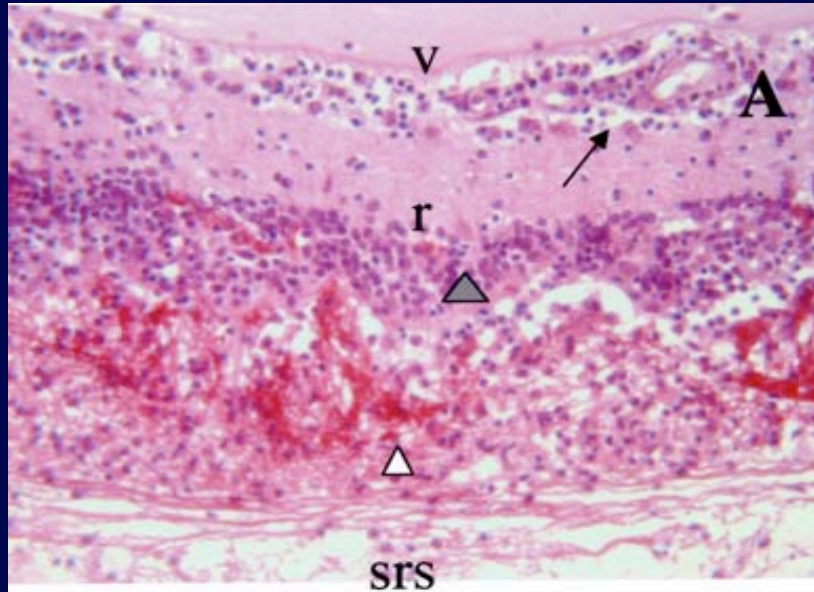
+ ED1/ED2 ET OX42: LES
CELLULES INFLAMMATOIRES
SONT ROUGES
+ LES ASTROCYTES SONT
ROUGES
+ LES NANOPARTICULES
SONT VERTES
+ COLOCALISATION JAUNE

EFFICACITE CLINIQUE DU TAMOXIFENE ET DU TAMOXIFENE VECTORISE PAR NANOPARTICLES DE PEG-PHDCA

(Y. de Kozak, K. Andrieux, H. Villarroya, C. Klein, B. Thillaye-Goldenberg, MC. Naud, E. Garcia , P.Couvreur, Europ J Immunol., 2004)

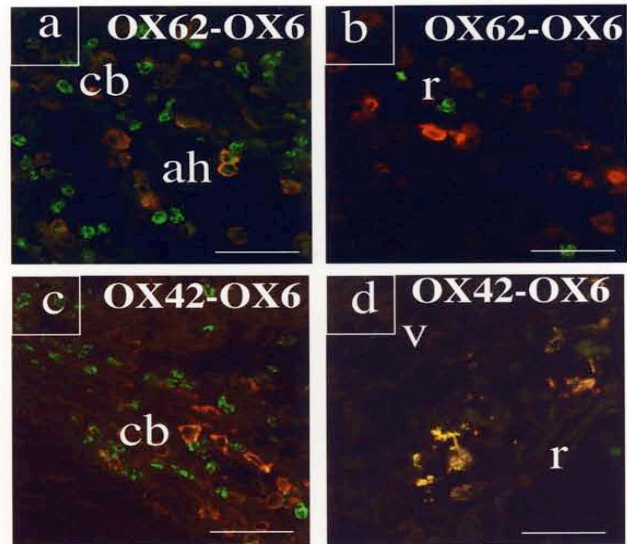


HISTOLOGIE APRES ADMINISTRATION IVT DE TAMOXIFENE LIBRE (A) OU DE TAMOXIFENE VECTORISE PAR DES NANOPARTICULES DE PEG-PHDCA (B)

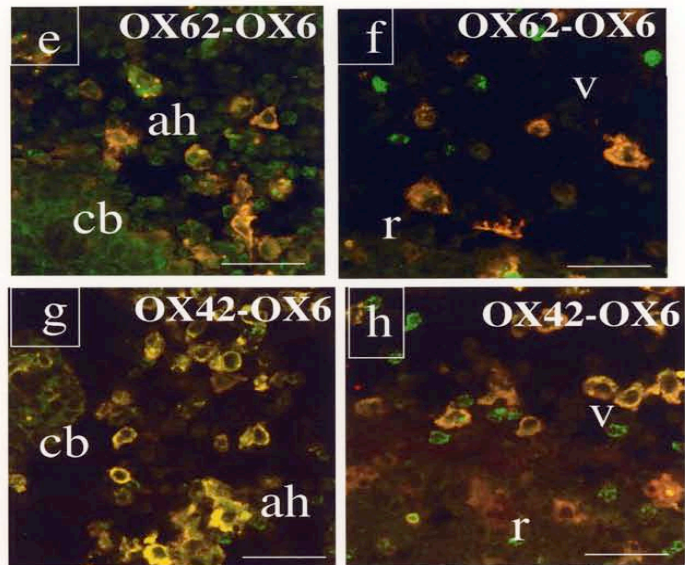


(Y. de Kozak, K. Andrieux, H. Villarroya, C. Klein, B. Thillaye-Goldenberg, MC. Naud, E. Garcia, P. Couvreur, *Europ J Immunol.*, 2004)

A NP-PEG-TAM



B NP-PEG



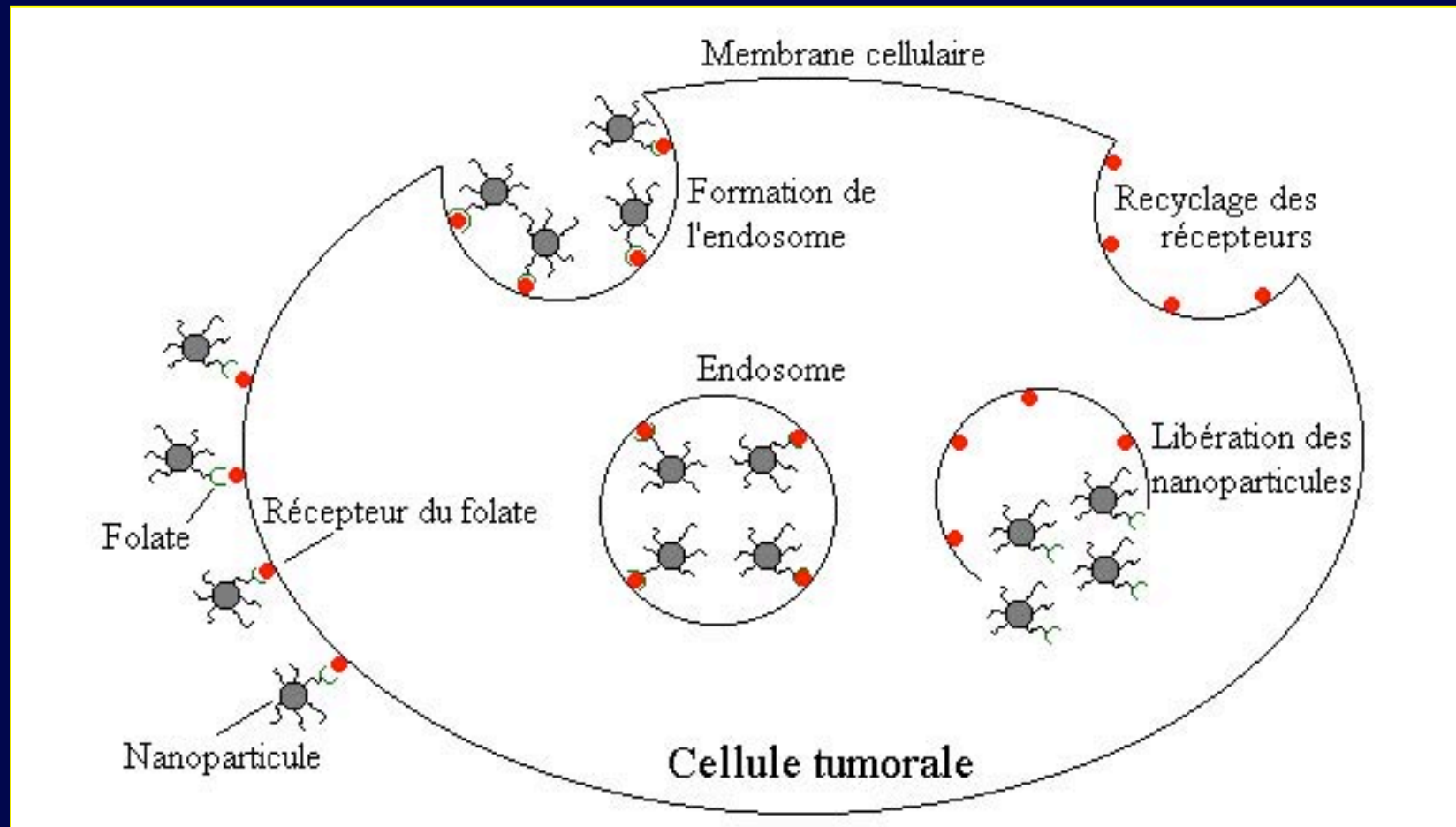
**EXPRESSION
IMMUNOHISTOCHIMIQUE
DE MHC Class II (OX 6)**

(Y. de Kozak, K. Andrieux, H. Villarroya, C. Klein,
B. Thillaye-Goldenberg,
MC. Naud, E. Garcia , P.Couvreur, Europ J
Immunol., 2004)

COMMENT ENTRER DANS LA CELLULE?

GRÂCE A DES
NANOTECHNOLOGIES EQUIPEES
DE MISSILES « MOLECULAIRES »

CIBLAGE TUMORAL PAR LE RECEPTEUR DE L'ACIDE FOLIQUE

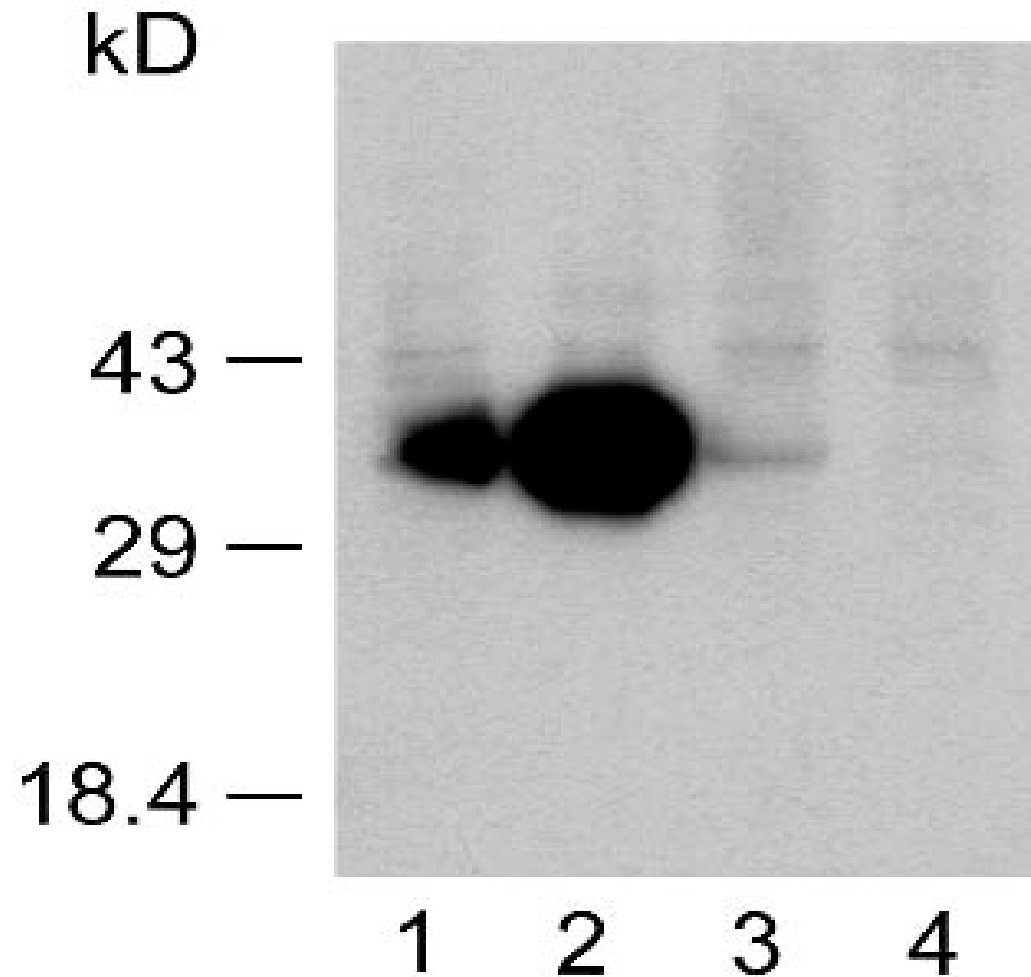


(B. Stella, S. Arpicco, M.T. Peracchia, D. Desmaele, J. Hoebcke, M. Renoir, J. d'Angelo, L. Cattel, P. Couvreur, J. Pharm. Sci., 2000)

WESTERN BLOT

B. Stella, P. Couvreur, M. Renoir, non publié

- 1 : IGROV1
- 2 : KB 3-1
- 3 : Ishikawa
- 4 : MCF7

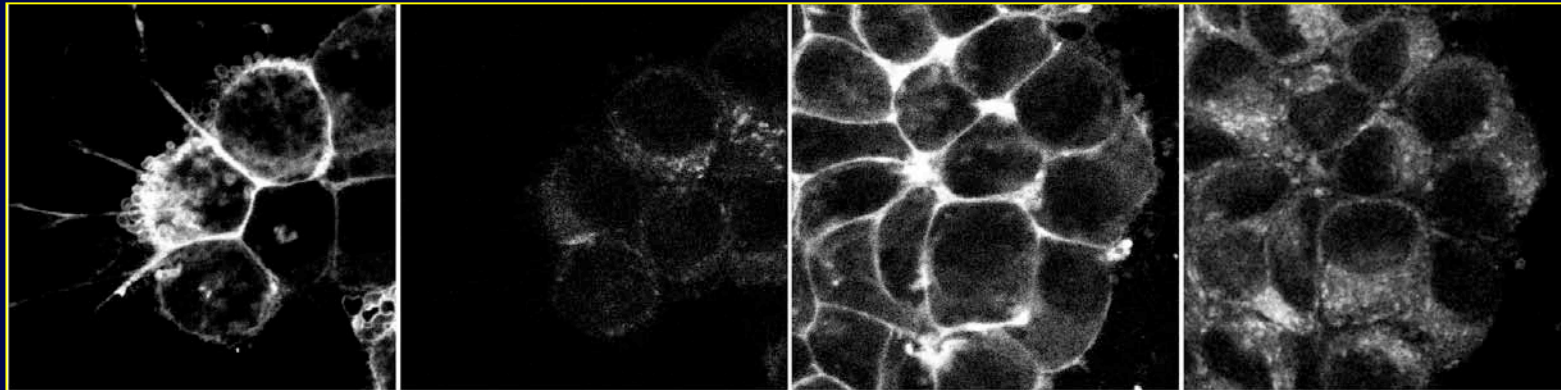


CIBLAGE CELLULAIRE

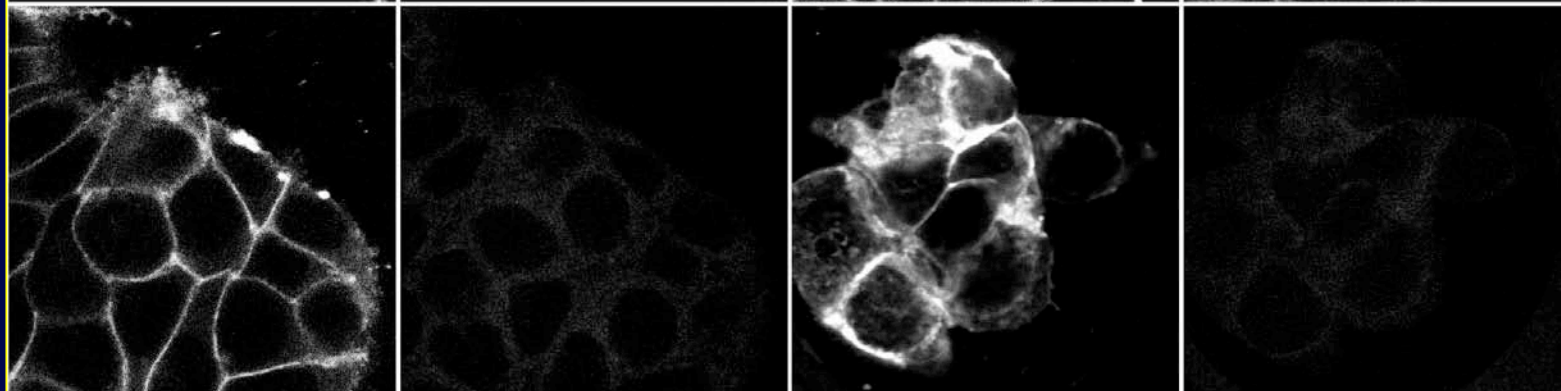
Nanoparticles

Folate-nanoparticles

KB



MCF7



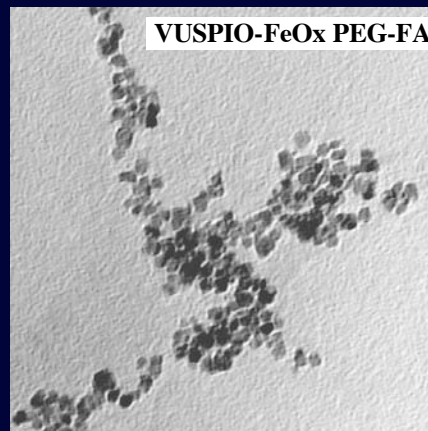
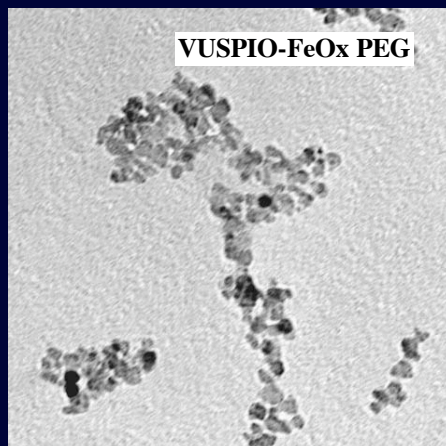
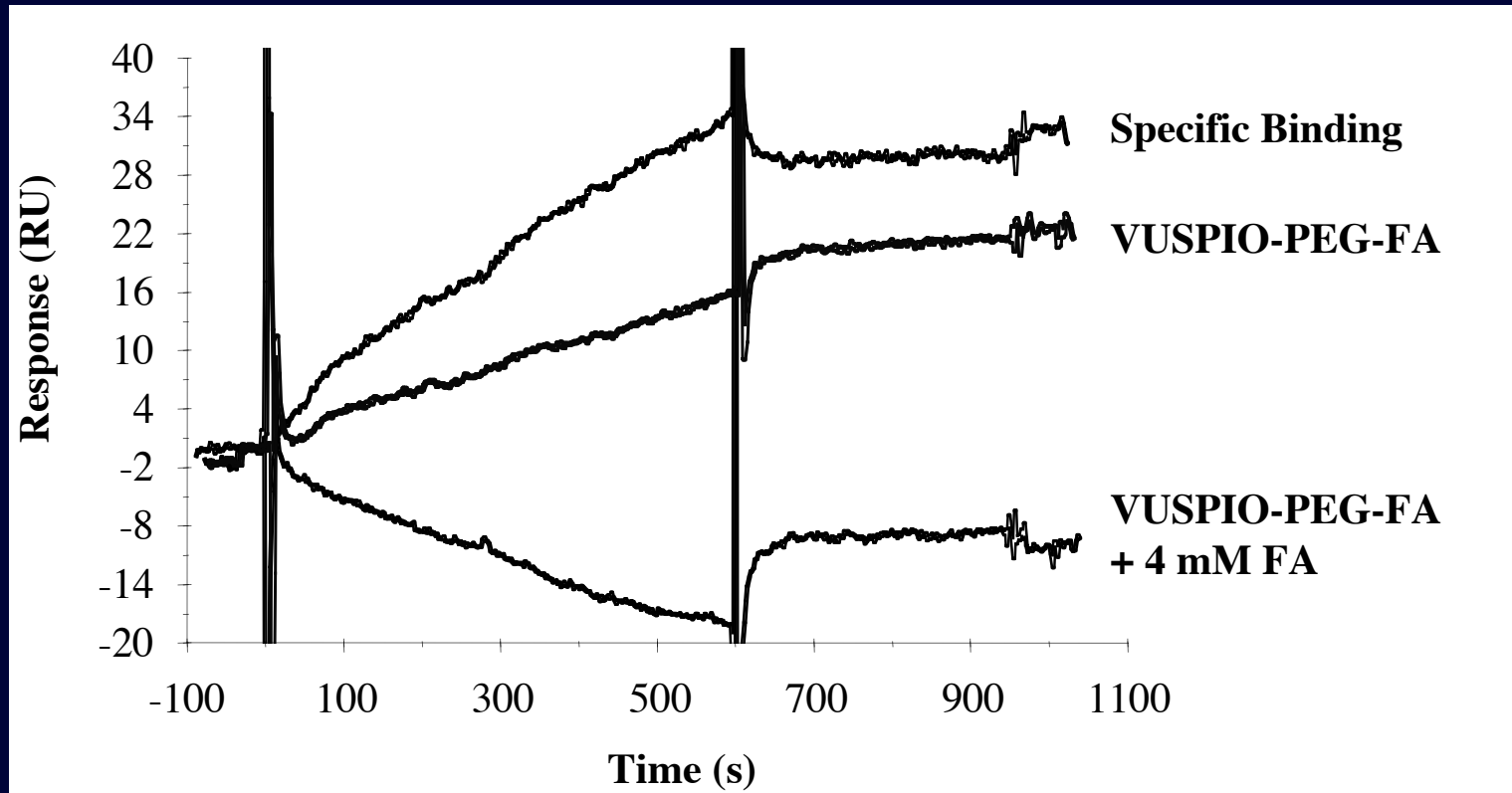
Membrane
labelling

Nanoparticles
fluorescence

Membrane
labelling

Nanoparticles
fluorescence

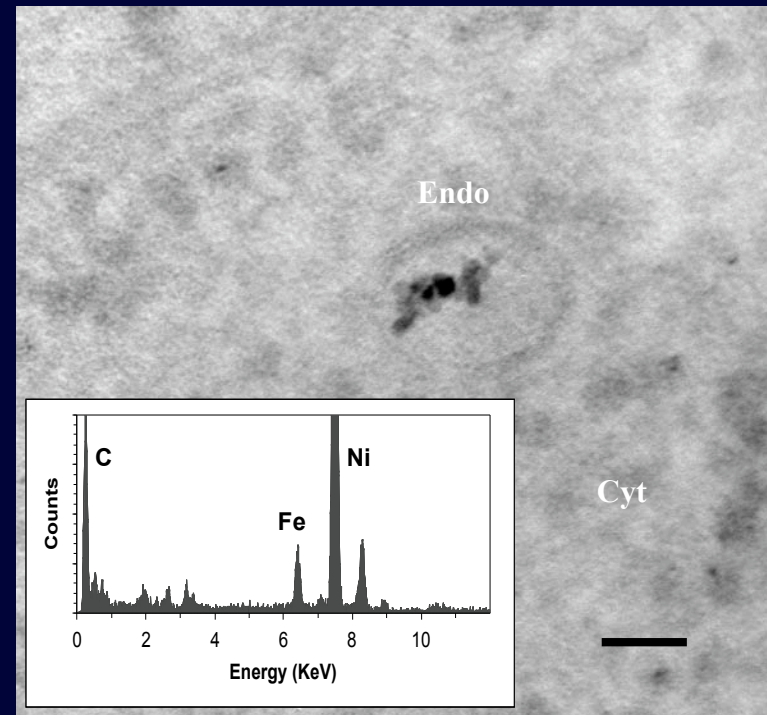
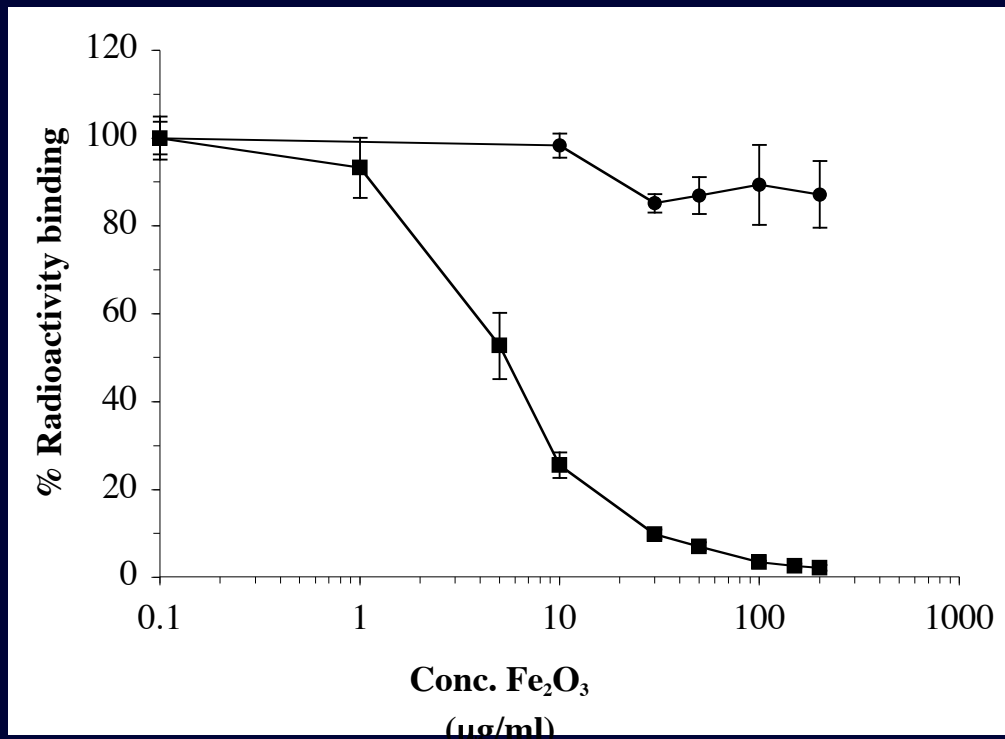
NANOPARTICLES D'OXYDE DE FER DECOREES AVEC L'ACIDE FOLIQUE

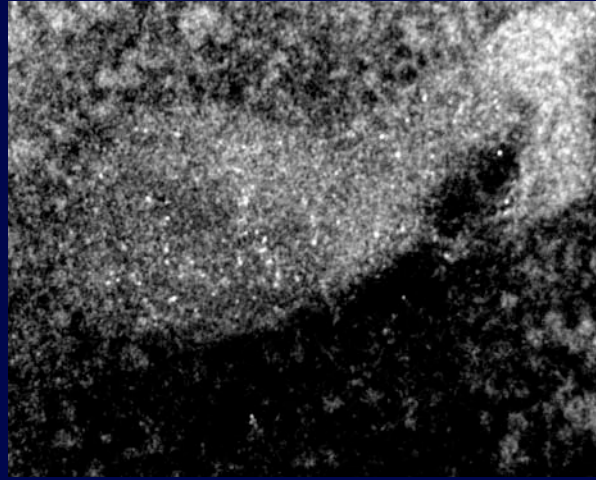
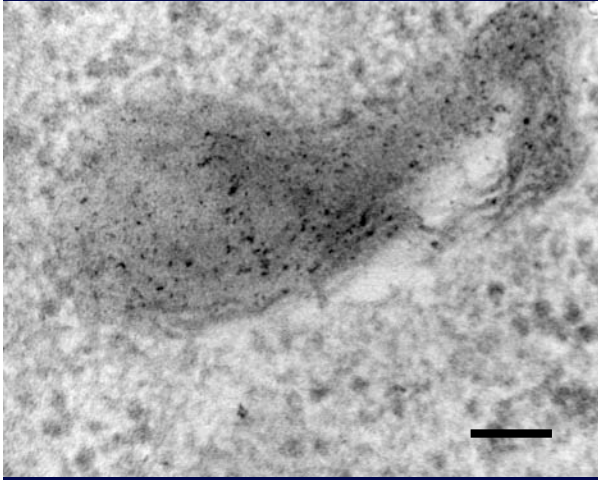


F. Sonvico, S. Mornet, S. Vasseur
C. Dubernet, D. Jaillard, J. Degrouard
J. Hoebeke, E. Duguet, P. Colombo,
P. Couvreur, *Bioconj. Chemistry*, 2005

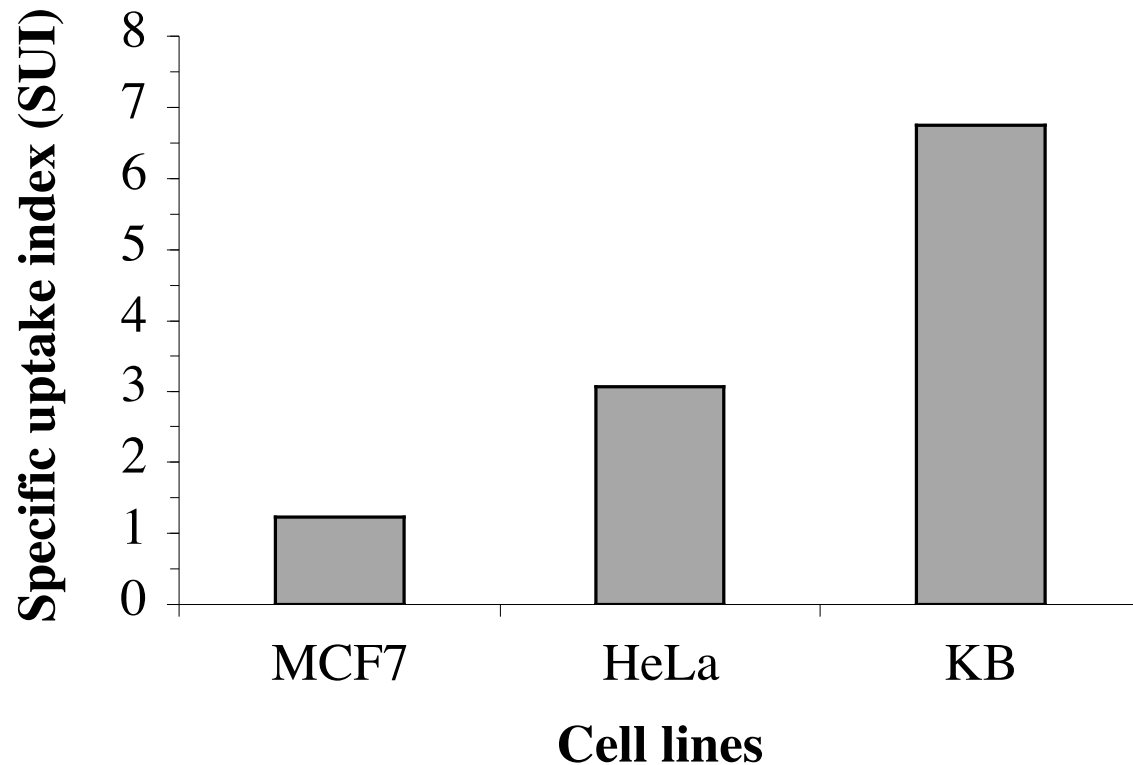
Inhibition compétitive de la capture de l'acide folique tritié et microscopie électronique haute résolution après capture cellulaire (cellules KB)

F. Sonvico, S. Mornet, S. Vasseur, C. Dubernet, D. Jaillard, J. Degrouard, J. Hoebeke, E. Duguet, P. Colombo, P. Couvreur, *Bioconj. Chemistry*, 2005





Electron diffracting maghemite crystals appear as bright spot in the right image.



NANOPARTICULES DE FER ET HYPERthermie SELECTIVE

F. Sonvico, S. Mornet, S. Vasseur
C. Dubernet, D. Jaillard, J. Degrouard
J. Hoebeke, E. Duguet, P. Colombo,
P. Couvreur, *Bioconj. Chemistry*, 2005

REMERCIEMENTS

- DE KOZAK (INSERM, Paris)
- G. VASSAL (IGR, Villejuif)
- C. MALVY (IGR, Villejuif)
- L BARRAUD, C. TREPO (INSERM, Lyon)
- E. DUGUET (Bordeaux)

- UMR CNRS 8612
- H. ALPHANDARY
- K. ANDRIEUX
- M. APPEL
- I. BRIGGER
- P. CALVO
- H. CHACUN
- C. DUBERNET
- E. FATTAL
- R. GREF
- M-T PERACCHIA
- M. RENOIR
- C. VAUTHIER
- BIOALLIANCE

