NANOMEDICAMENTS ET ENJEUX PHARMAKOCINETIQUES

Développement d'un cytotoxique:

Le Nab-Paclitaxel, Abraxane®

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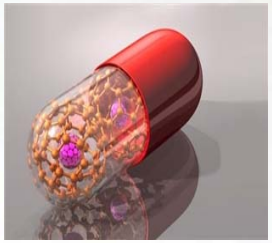
Inserm S_911 & APHM

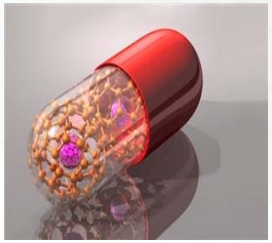


Nanotechnologies

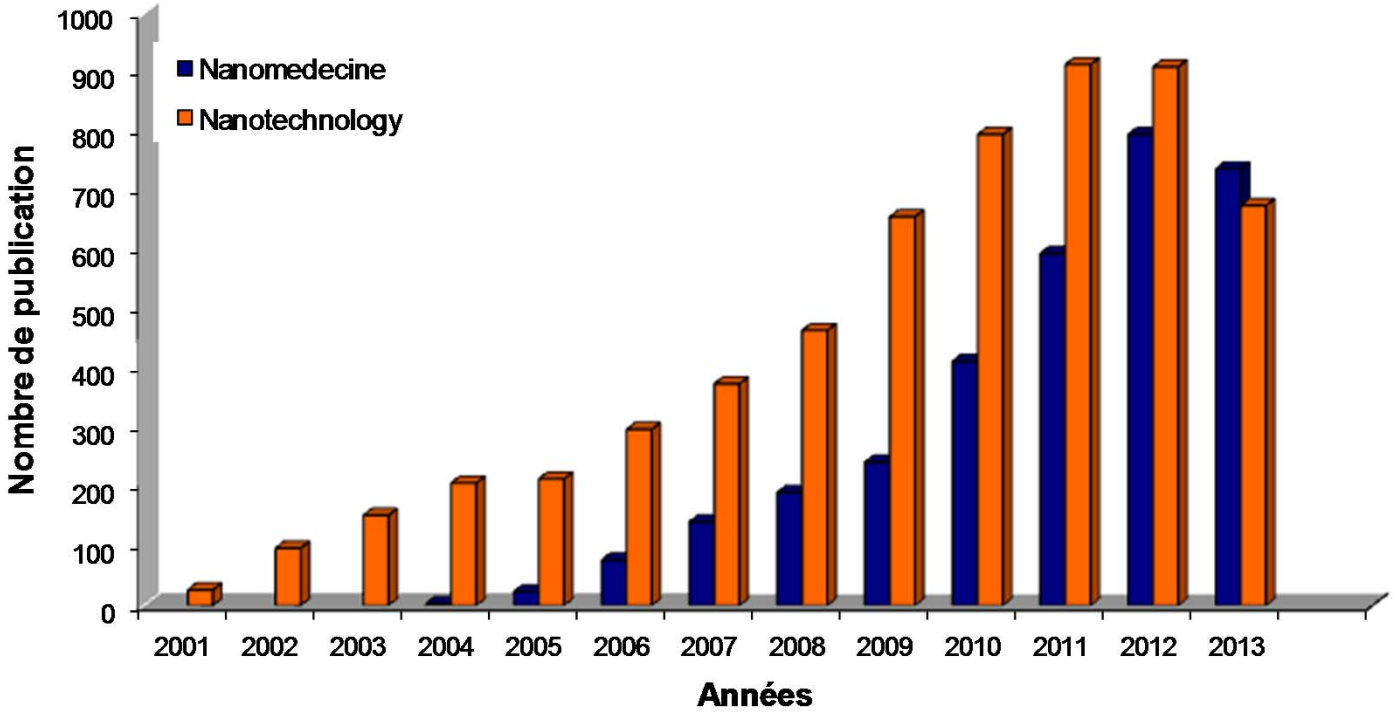
« Tout objet manufacturé dont la dimension s'exprime en nanomètres »

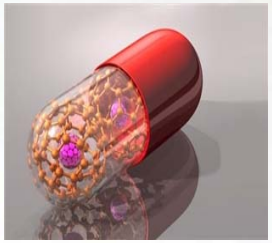
5 000 000 nm

2 nm



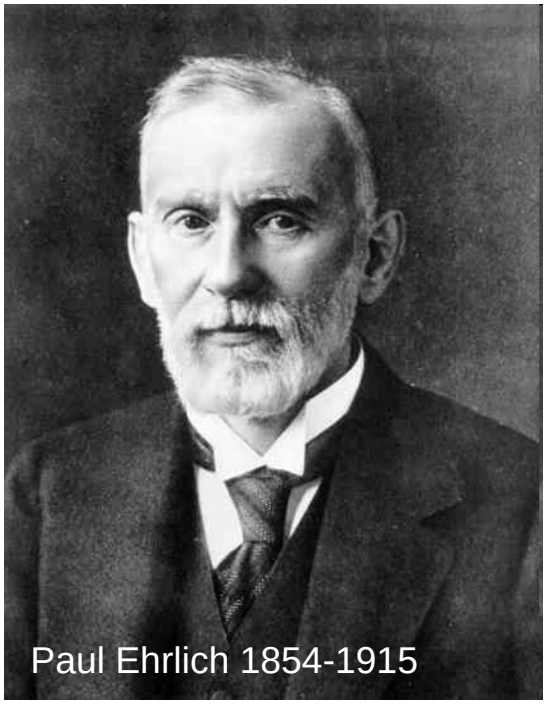
Nanotechnologies



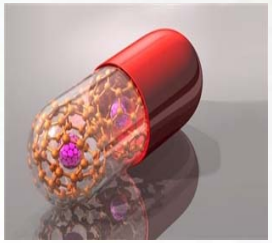


Nanomédicament

Concept de la « Magic Bullet »

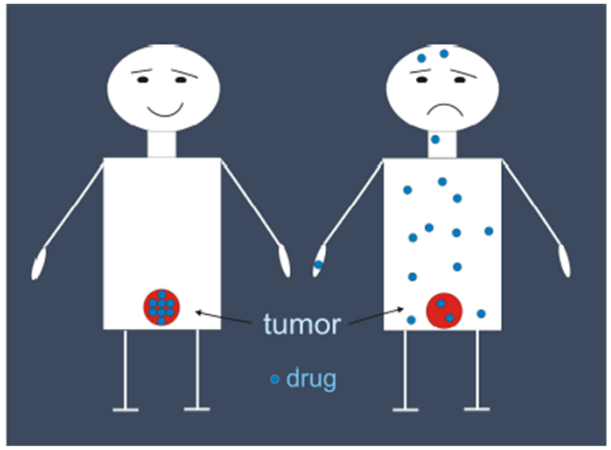


« Comment améliorer l'accès des principes actifs au siège de la pathologie? »



Objectif des Nanomédicaments

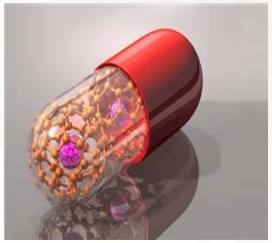
- Améliorer les caractéristiques physico-chimiques des molécules
- Protection des dégradations enzymatiques
- Contrôler la libération de la molécule



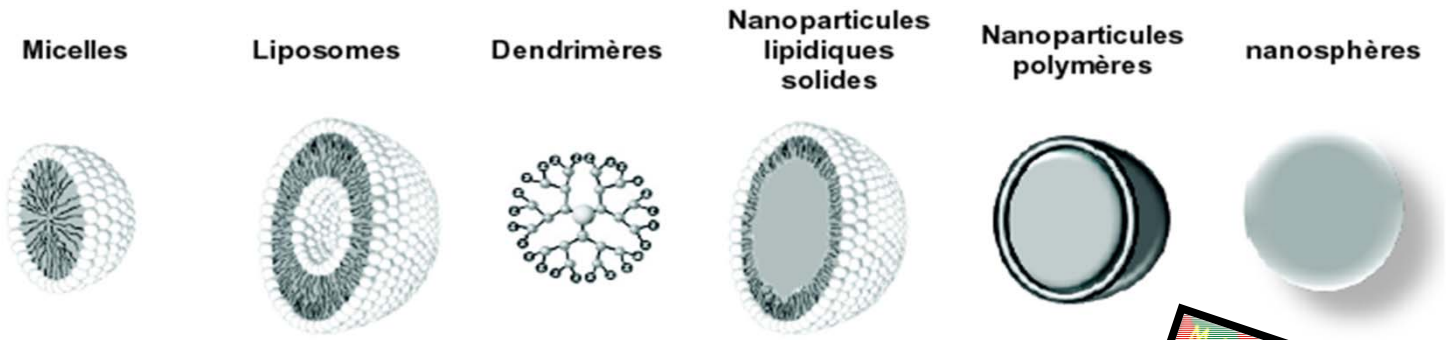
Efficacité

Toxicité

Améliorer l'index thérapeutique



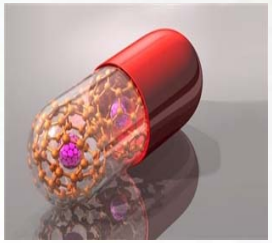
1. Particules au sein desquelles sont encapsulées les actifs : les encapsulées



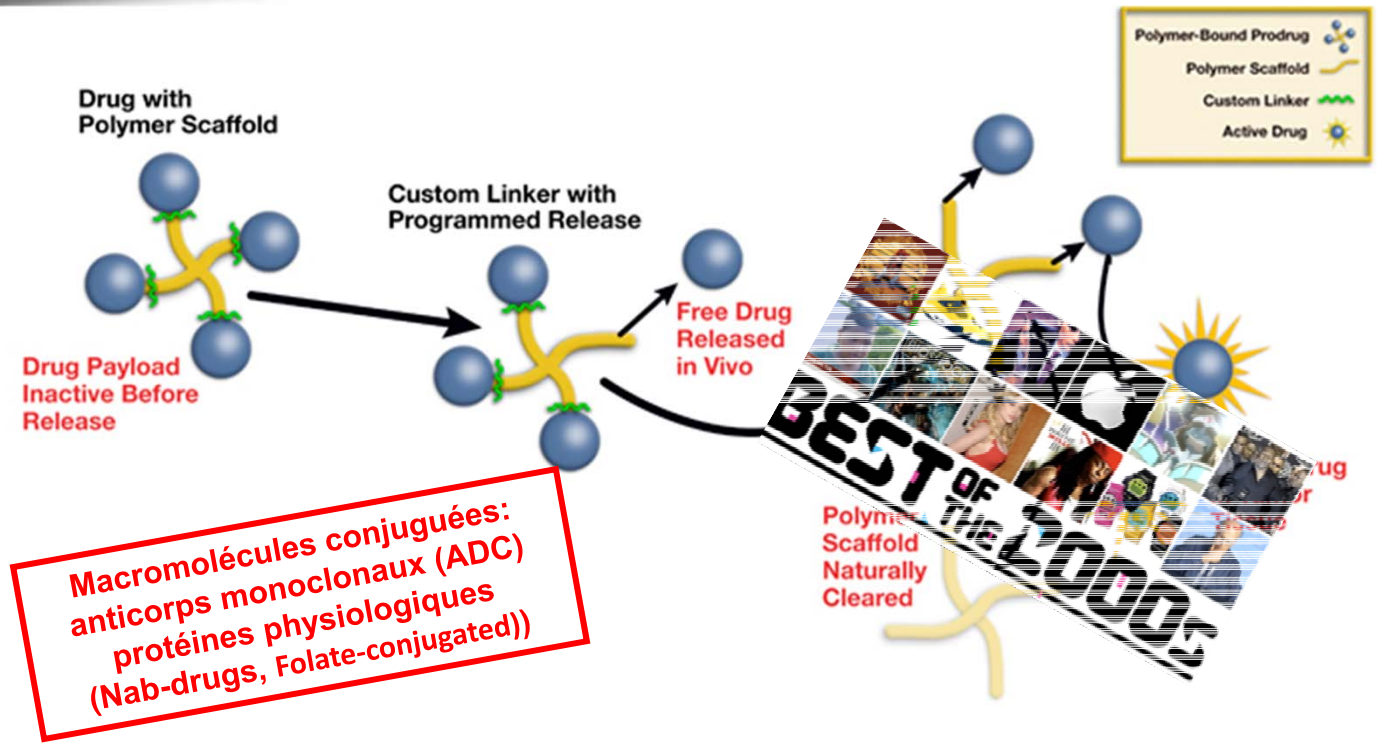
Ces particules sont caractérisées par :

- leur taille
- leur forme sphérique
- leur biocompatibilité
- leur taux d'encapsulation

Aujourd'hui, les liposomes constituent > 90% des formes disponibles en oncologie

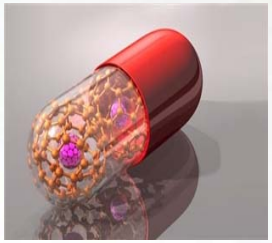


2. Vecteurs auxquels sont greffés directement les actifs via des linkers : les conjugués

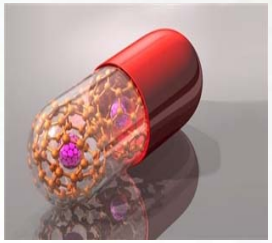


Ces vecteurs sont caractérisés par la charge utile transportée (« *payload* »)

Fixer les principes actifs à des macromolécules permet de guider la distribution vers le tissu cible !

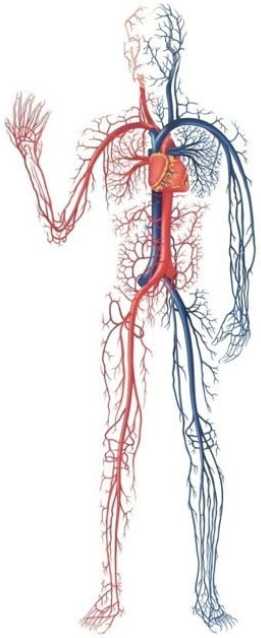


3. Nanotechnologies & machines : Nanobots

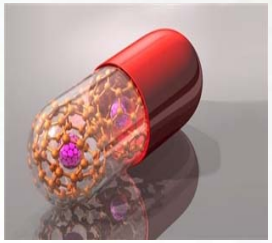


Nanotechnologies & substances actives

Les nanotechnologies ne visent pas à toucher de nouvelles cibles pharmacologiques mais à augmenter la spécificité anti tumorale des traitements

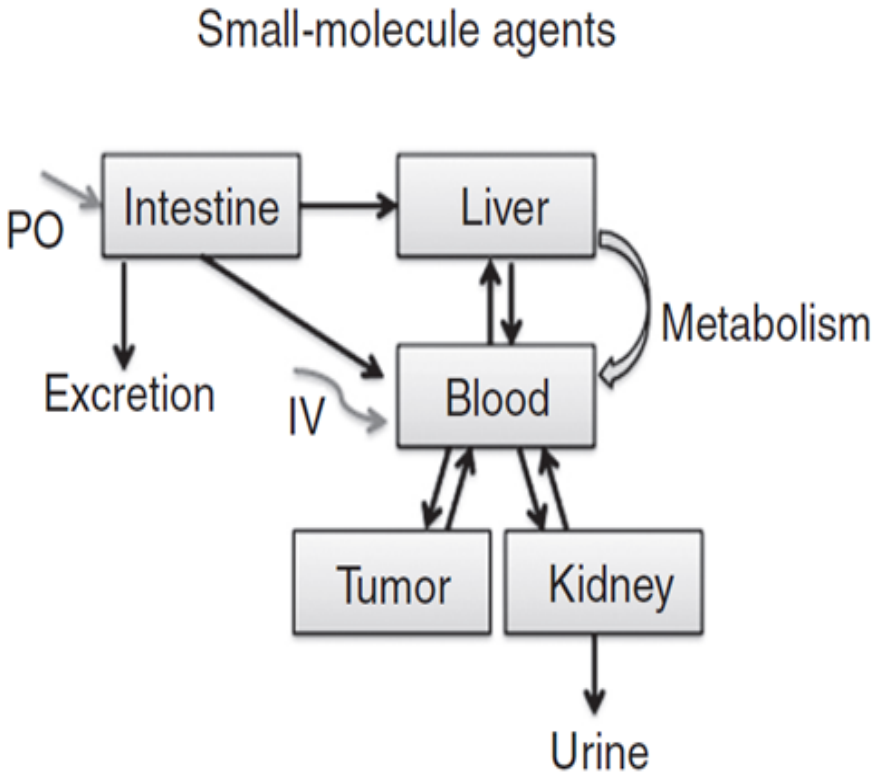


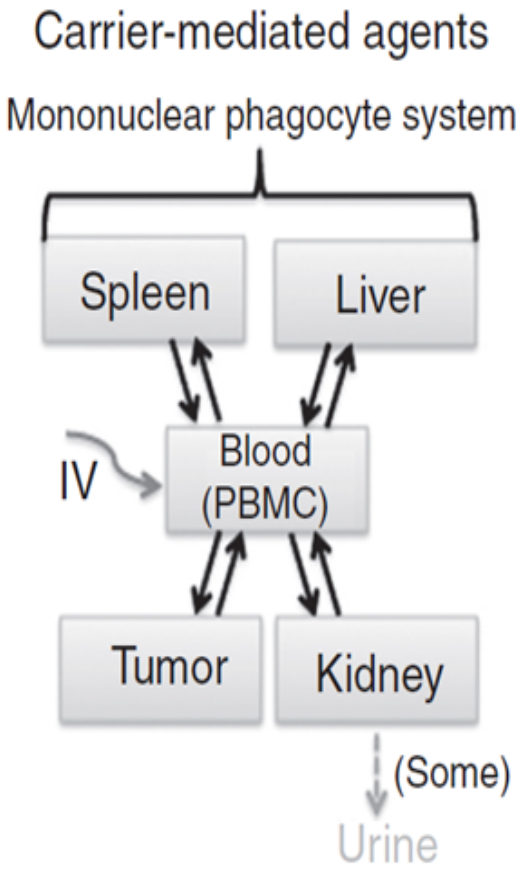
Les bénéfices thérapeutiques reposent sur une amélioration des profils pharmacocinétiques permettant une meilleure réponse pharmacodynamique

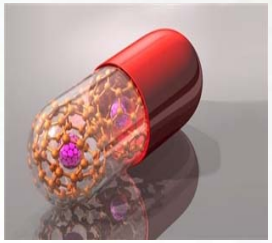


Nanotechnologies et enjeux pharmacocinétiques

Des schémas pharmacocinétiques différents







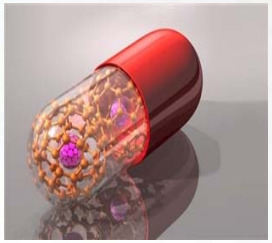
Nanotechnologies et enjeux pharmacocinétiques

	Free DOX	Myocet (non-pegylated liposomal DOX)	Doxil/Caelyx (pegylated liposomal DOX)
Dose (mg/kg)	1.2	1.8	1.5
AUC (mg.h/L)	3.5	19.4	4082
Clearance (ml/h)	25'300	9'520	23
Vss (L)	365	139	3.0
Half-life (h)	0.06/10.4[a]	<1/52.6[a]	84

[a]Two elimination phases.

Gabizon et al, Cancer Res 1994
Huwyler J et al. Int Journal of Nanomedecine 2008

1 Forme vectorielle = 1 pharmacocinétique



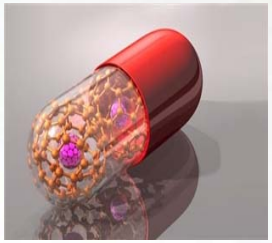
Nanotechnologies et enjeux pharmacocinétiques

Que dose t'on ?

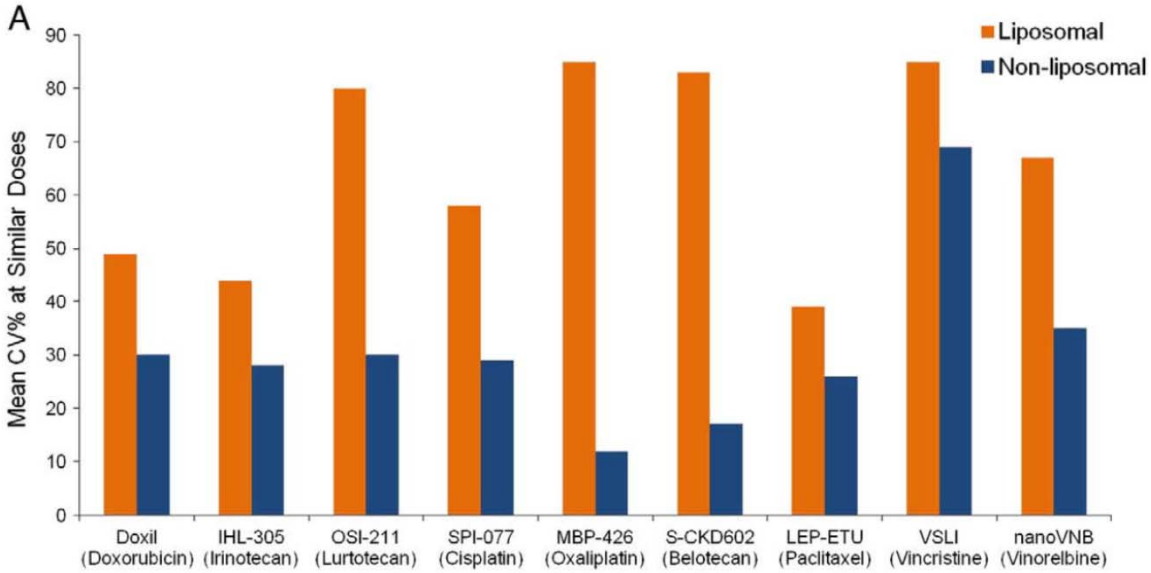
Total

Vecteur

Drogue libre

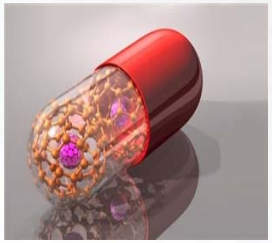


Nanotechnologies et enjeux pharmacocinétiques



Schell RF and al, Nanomedicine 2014

Grande variabilité inter individuelle !



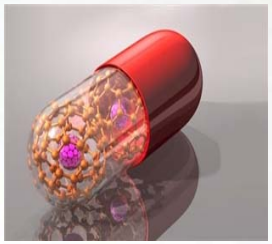
Nanotechnologies et enjeux pharmacocinétiques

1.Propriétés des vecteurs (PK systémique)

- Stabilité
- Taille vésiculaire
- Propriétés de surface
- Furtivité
- Charge électrique
- Pharmacocinétique
- Accumulation dans l'organisme

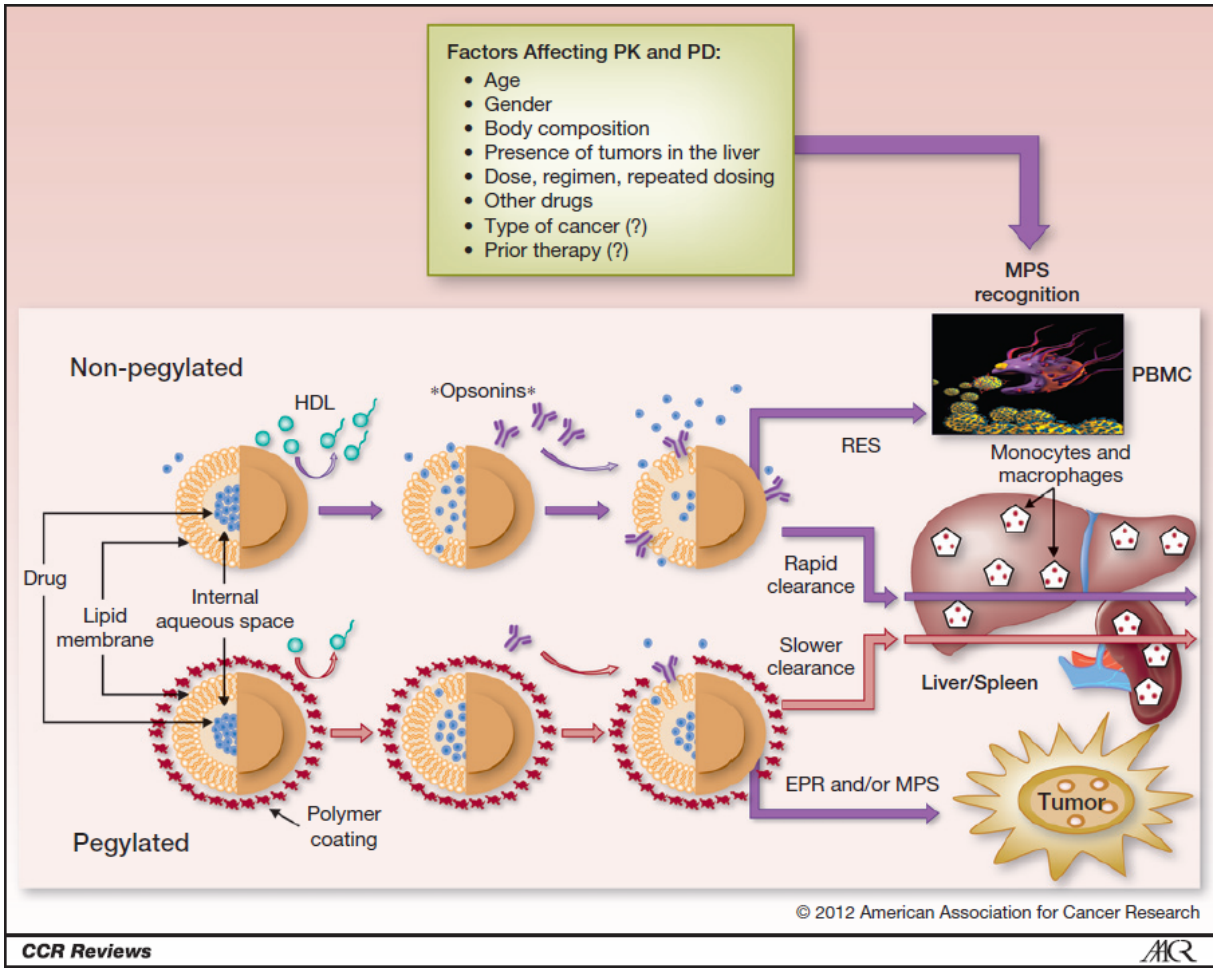
2. Facteurs tumoraux (PK tumorale)

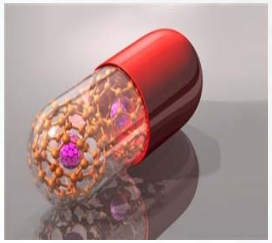
- Variation du flux sanguin
- Perfusion diminuée
- Perméabilité vasculaire augmentée
- Pression interstitielle diminuée
- Activité de phagocytose réduite



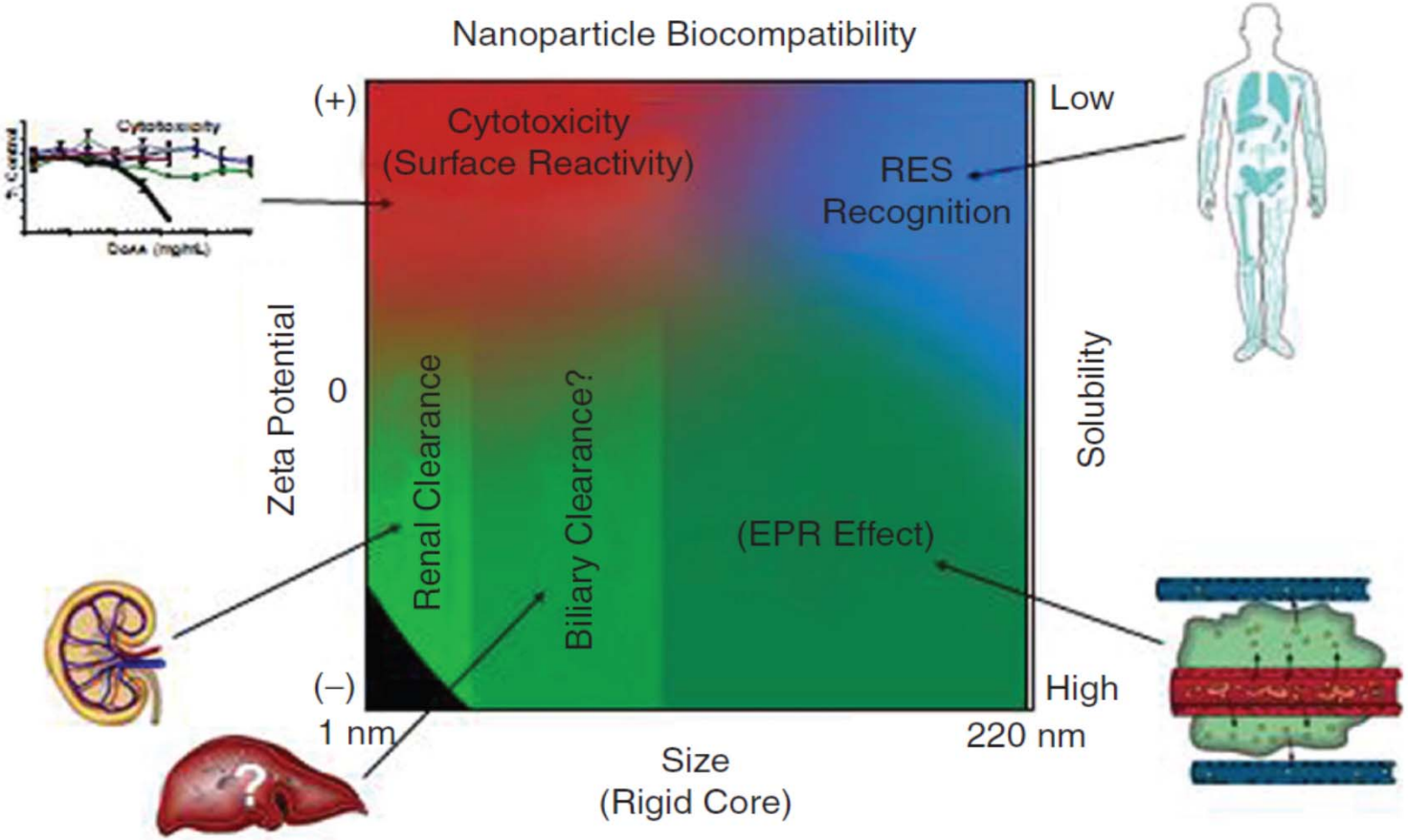
Nanotechnologies et enjeux pharmacocinétiques

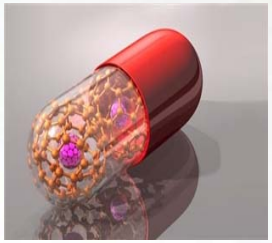
3. Caractéristiques individuelles du patient





PK systémique: classification des nanoparticules



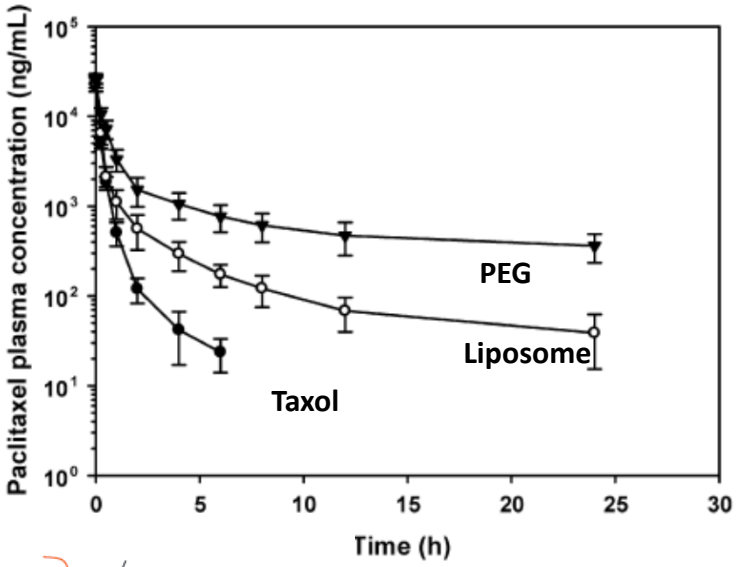


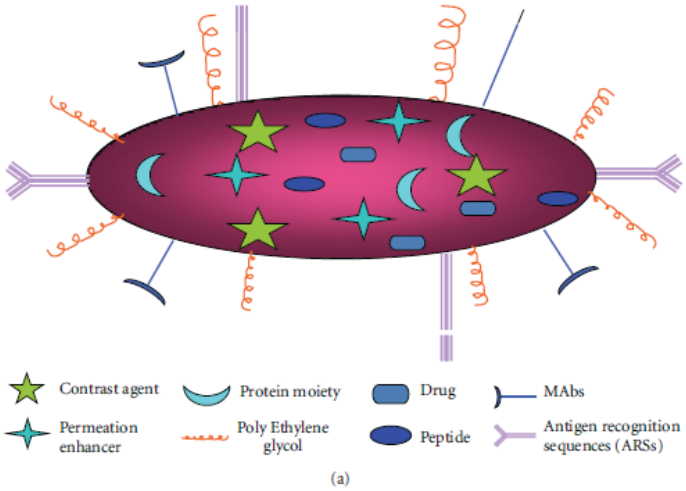
PK systémique: Caractéristiques du nanovecteur

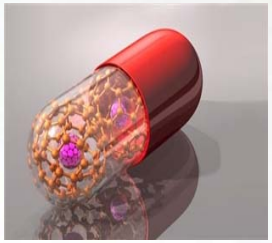
- Composition

(phospholipides, polymères)

- Nature du PA
- Charge de la particule
- Cholestérol
- PEG
- Ligand
- Taille



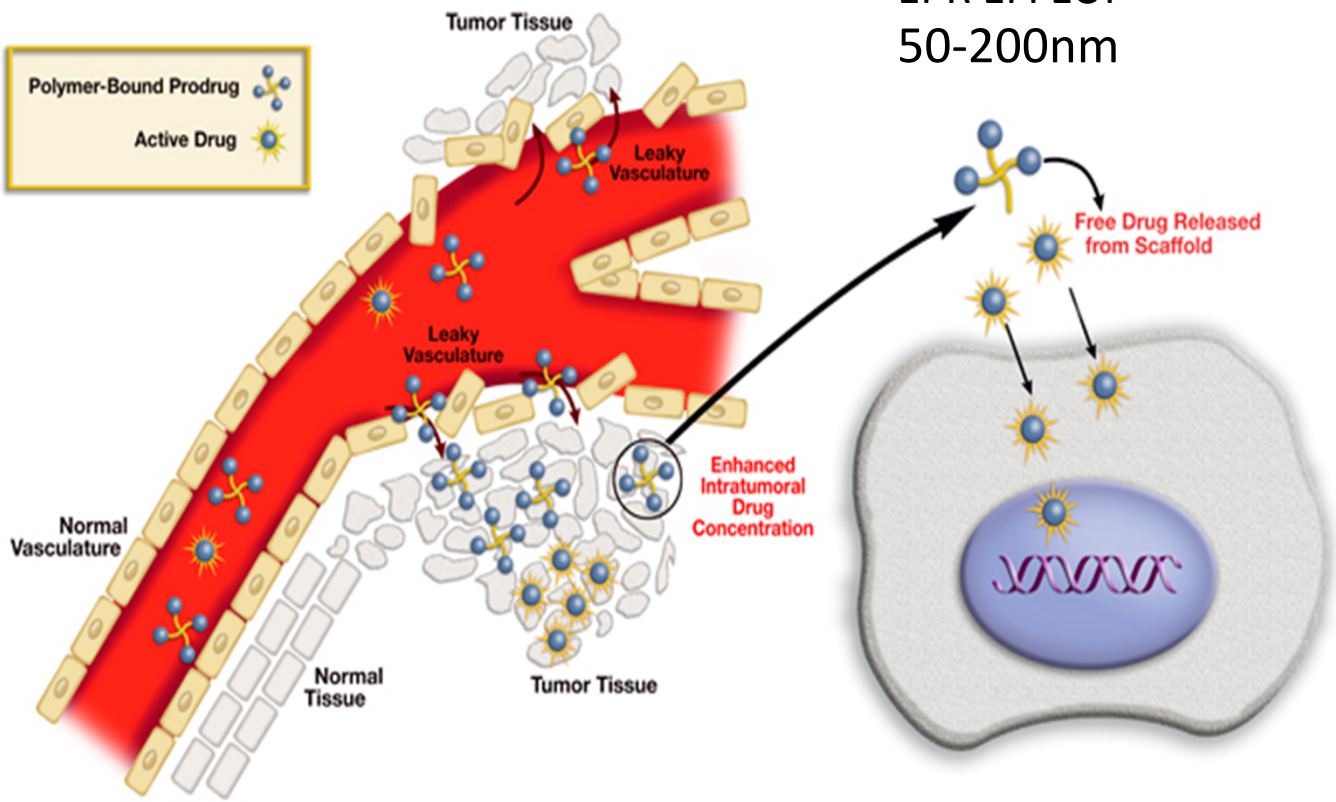


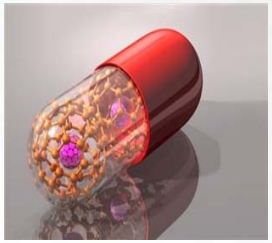


PK systémique:
Taille du nanovecteur

EPR effect « enhanced permeation and retention effect »

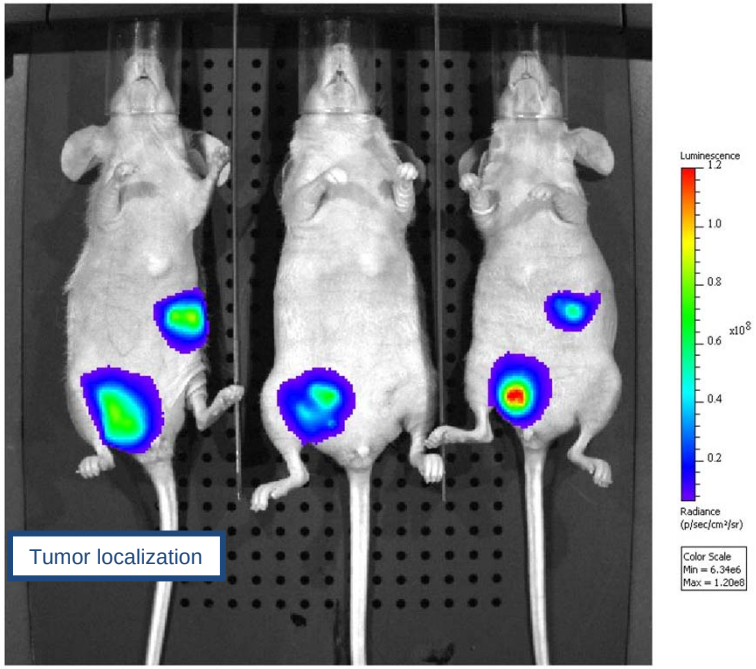
EPR EFFECT
50-200nm

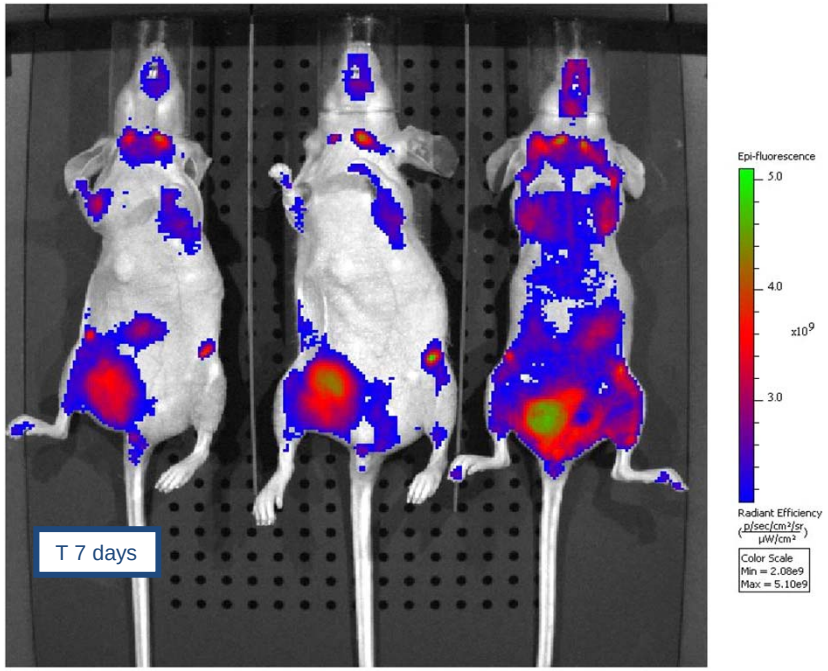




PK systemique: Accumulation tumorale

EPR effect « enhanced permeation and retention effect »

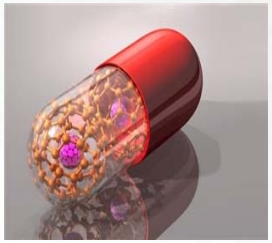




Localisation des tumeurs

Accumulation des particules

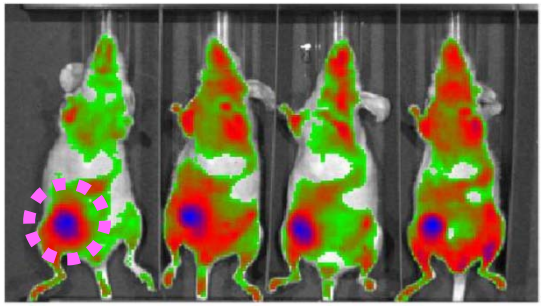
Fanciullino et al. Proc AACR 2012



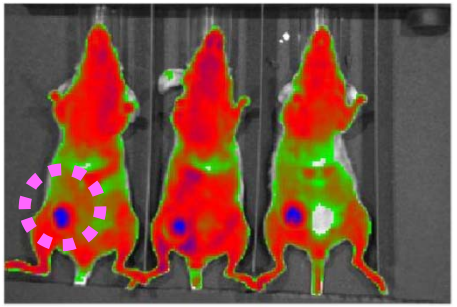
PK systemique: Accumulation tumorale

Pourquoi la taille compte!

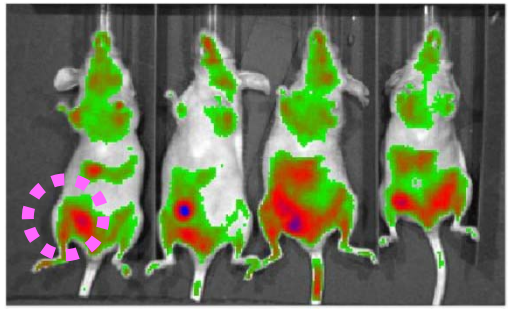
= localisation tumorale (MDA231-Luc+: sein)



50-80 nm



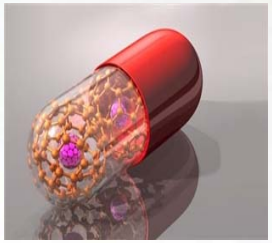
120 nm



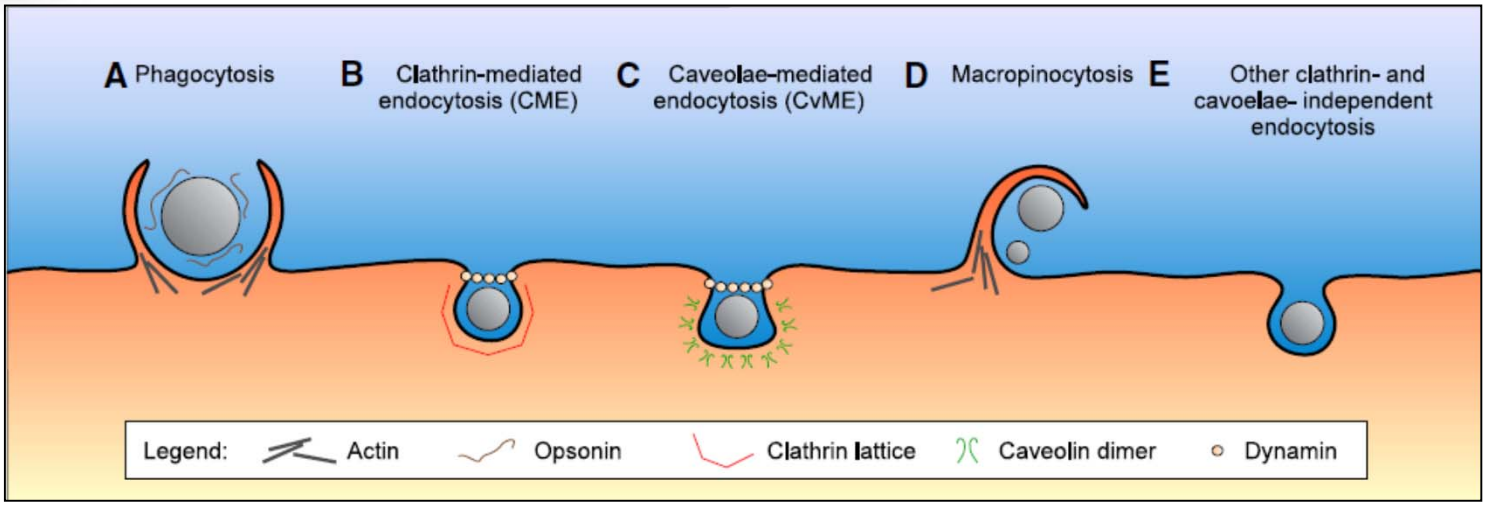
250 nm

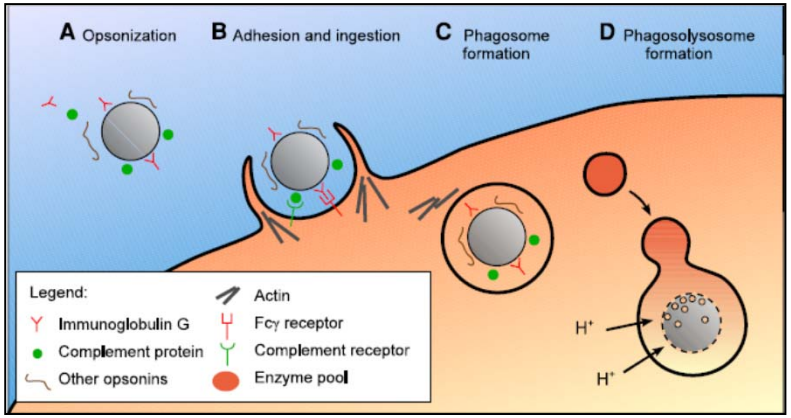
L'accumulation tumorale est d'autant plus importante que la taille de la particule est faible!

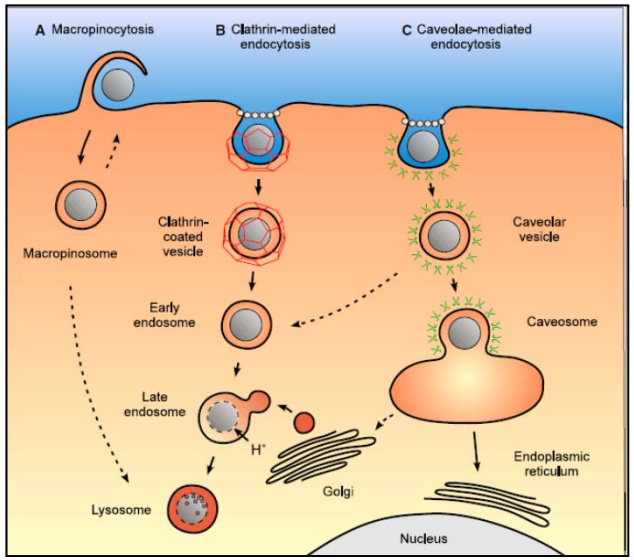
Fanciullino et al. Proc AACR 2012

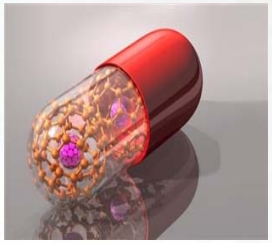


PK tumorale: Plusieurs voies de pénétration



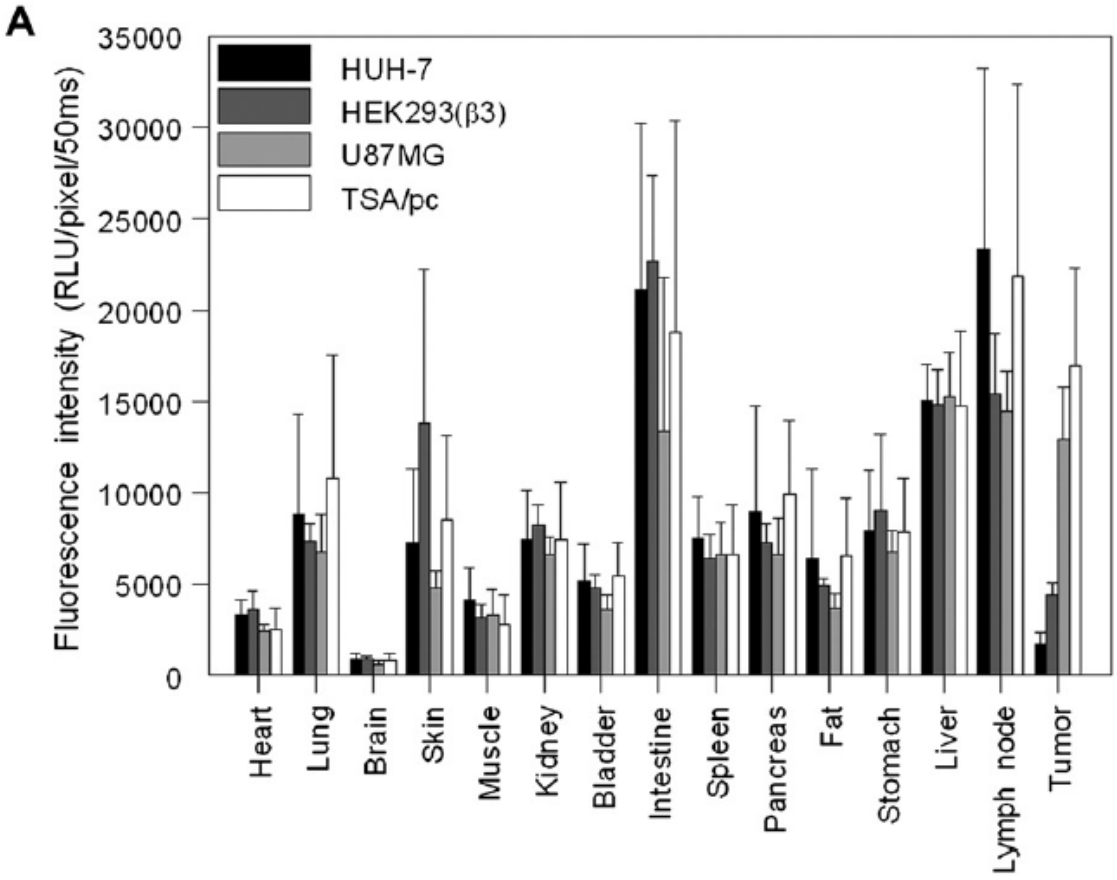




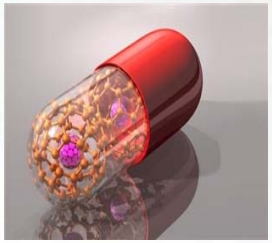


PK tumorale: Impact du type tumorale

LNC, 50nm



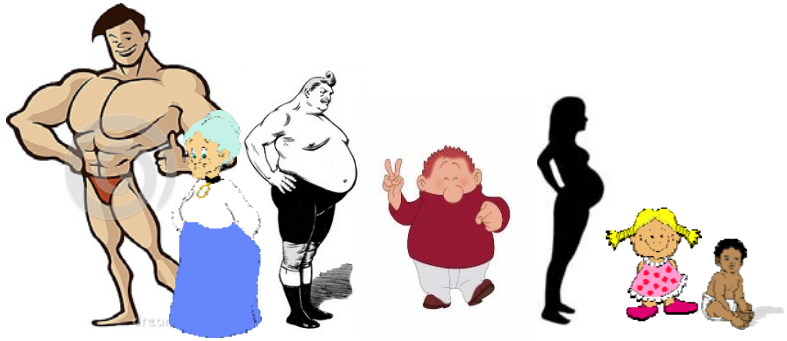
Impact de la tumeur sur l 'étape de distribution!



Caractéristiques individuelles du patient

Variabilité interindividuelle:

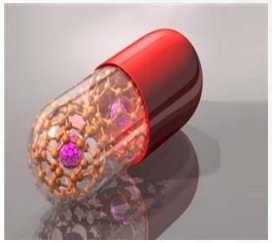
- Age
- Poids
- Sexe
- Masse corporelle
- Physiopathologie
- Antécédents …



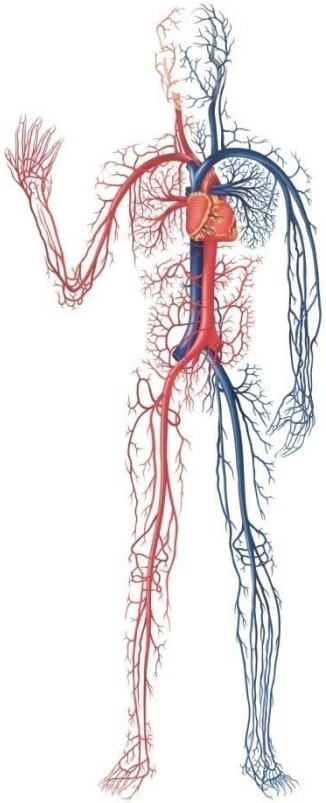
Impact de l'expression du système immunitaire

Influence du nombre de monocytes sur la clairance des nanovecteurs

Zamboni and al,
Liposome Research, 2011



Enjeux PK: Take-Home message!



FACTEURS INFLUENCANTS LA PK

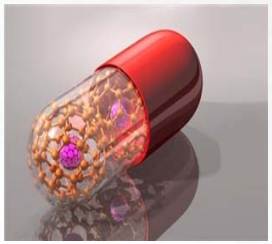
- Caractéristiques du vecteur
- Caractéristiques de la tumeur
- Caractéristiques individuelles

PROBLEMATIQUES DE BIOANALYSE

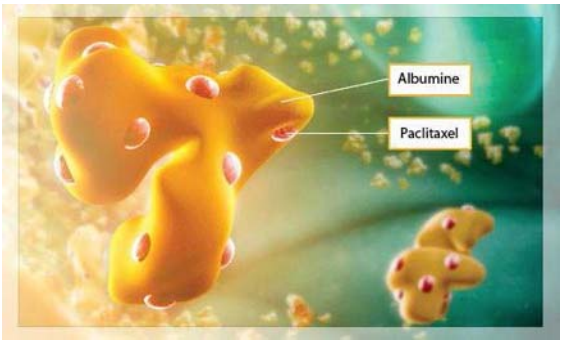
- Libre
- Encapsulée
- Total

QUELLE PK?

-Systémique
-Tumoral cellulaire



Nab-drugs: Nab-Paclitaxel



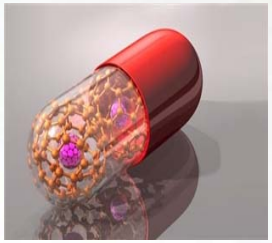
L'agent vecteur n'est pas un anticorps thérapeutique mais une protéine physiologique : l'albumine

↓

Permet d'acheminer des actifs très lipophiles

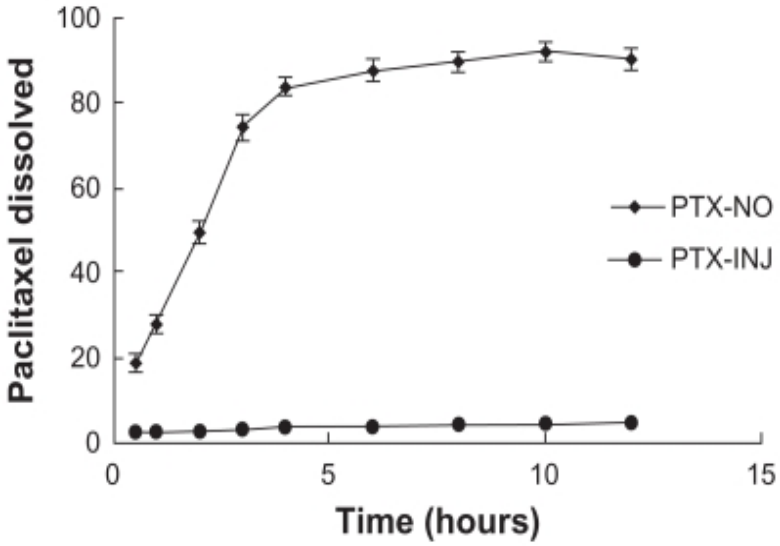
↓

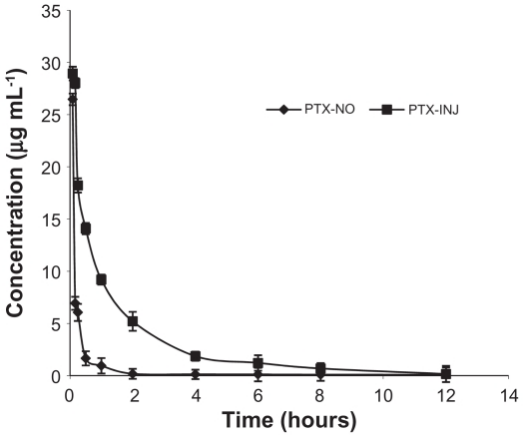
Permet un ciblage antitumoral passif (EPR) et actif (SPARC)



Nab-paclitaxel (Abraxane®)

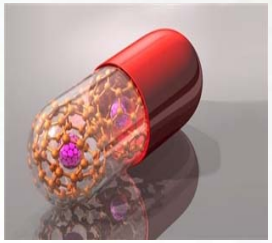
Etudes du profil pharmacocinétique





Parameters	PTX-NO	PTX-INJ
α/h^{-1}	4.177 ± 1.537^{a}	1.466 ± 0.366
β/h^{-1}	0.142 ± 0.049	0.204 ± 0.082
V_C, $L \cdot kg^{-1}$	0.748 ± 0.263	0.697 ± 0.271
$t_{1/2,\alpha}$, hours	0.1863 ± 0.077^{a}	0.495 ± 0.114
$t_{1/2,\beta}$, hours	5.646 ± 2.941	3.774 ± 1.352
$AUC_{0-\infty}$, $\mu g \cdot h \cdot mL^{-1}$	5.196 ± 1.426^{b}	20.343 ± 9.119
CL(s), $L \cdot kg^{-1} \cdot h^{-1}$	2.050 ± 0.616^{a}	0.556 ± 0.190
MRT, hours	3.199 ± 3.718	2.753 ± 0.943

Wang Y and al, Int J Nanomedicine, 2011



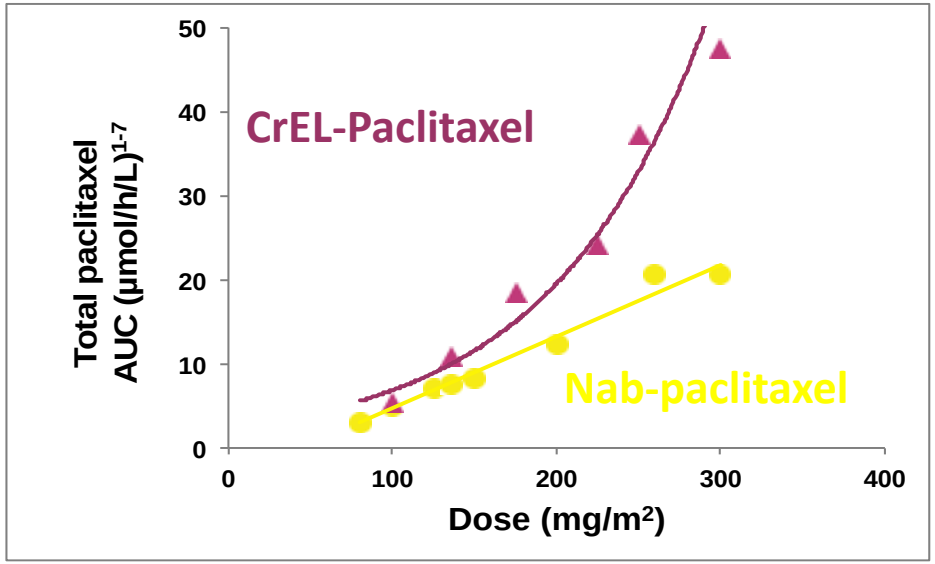
Nab-paclitaxel (Abraxane®)

Etudes du profil pharmacocinétique

Table 1.

Blood pharmacokinetic variables of paclitaxel formulated as either ABI-007 or Taxol

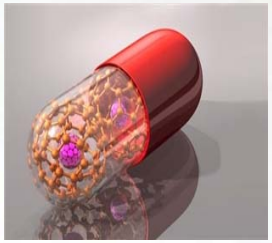
Variable	ABI-007*		Taxol*		
	5 mg/kg (Radioactivity)	5 mg/kg (HPLC)	5 mg/kg (Radioactivity)	5 mg/kg (HPLC)	10 mg/kg (Radioactivity)
$t_{1/2}$ (h)	19.01	11.42	20.78	7.24	7.58
T_{max} (h)	0.033	0.033	0.033	0.033	0.033
C_{max} (µg/mL)	4.2	4.0	13.5	11.8	32.3
C_0† (µg/mL)	8.1	7.3	20.5	17.7	40.2
AUC_{last} (µg·h/mL)	6.14	3.78	10.44	5.60	36.43
AUC_∞ (µg·h/mL)	9.86	4.59	15.69	5.85	41.13
$AUC_{\infty\%extrap}$ (%)	37.80	17.6	33.4	4.3	11.4
V_z (L/kg)	14.18	18.33	9.36	8.75	2.66
CL (L/h·kg)	0.517	1.112	0.312	0.837	0.243



CL et VD supérieurs

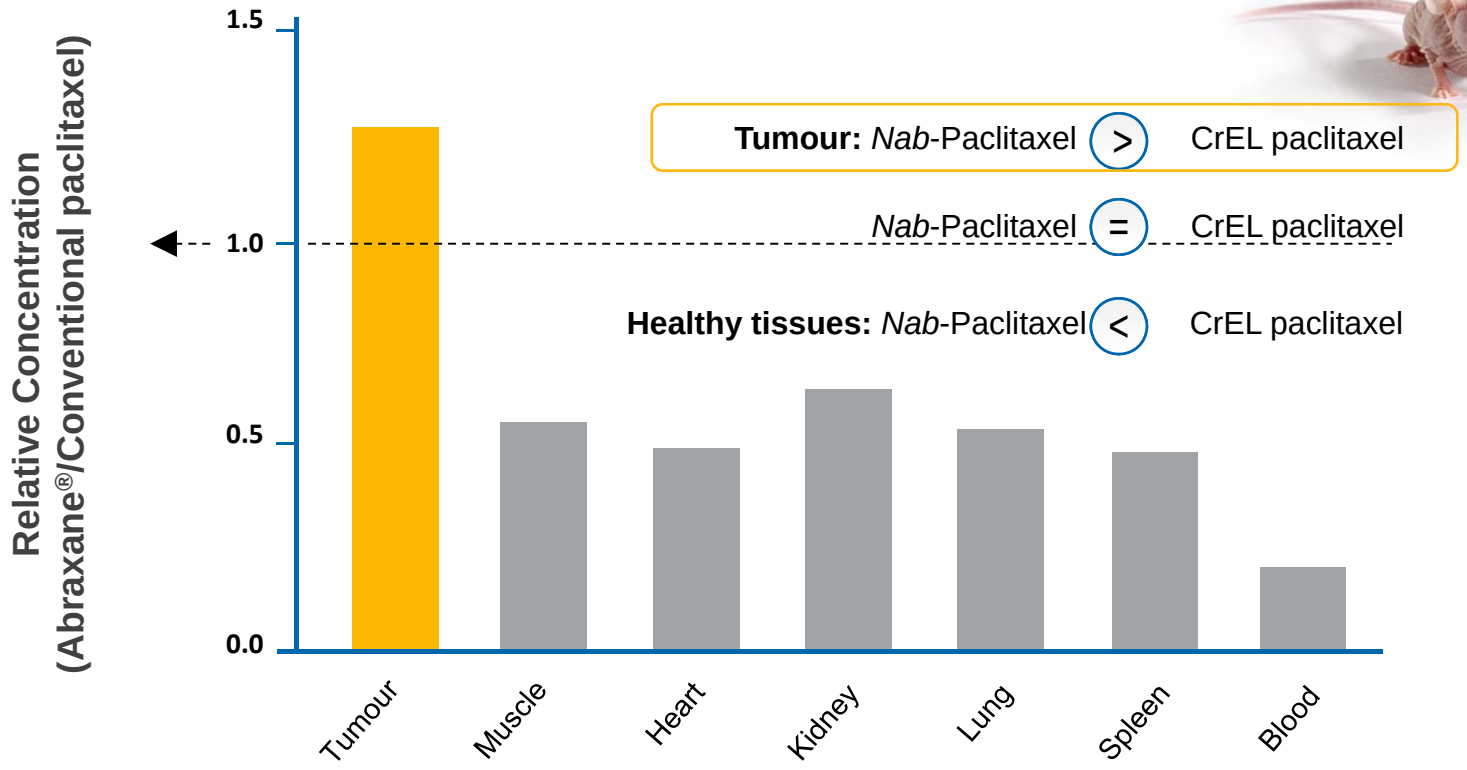
Le paclitaxel conjugué présente une PK linéaire

Sparreboom and al, Clinical Cancer Research, 2005



Nab-paclitaxel (Abraxane®)

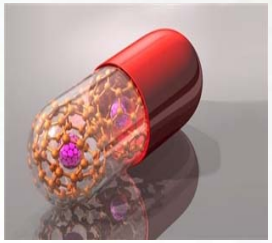
PK



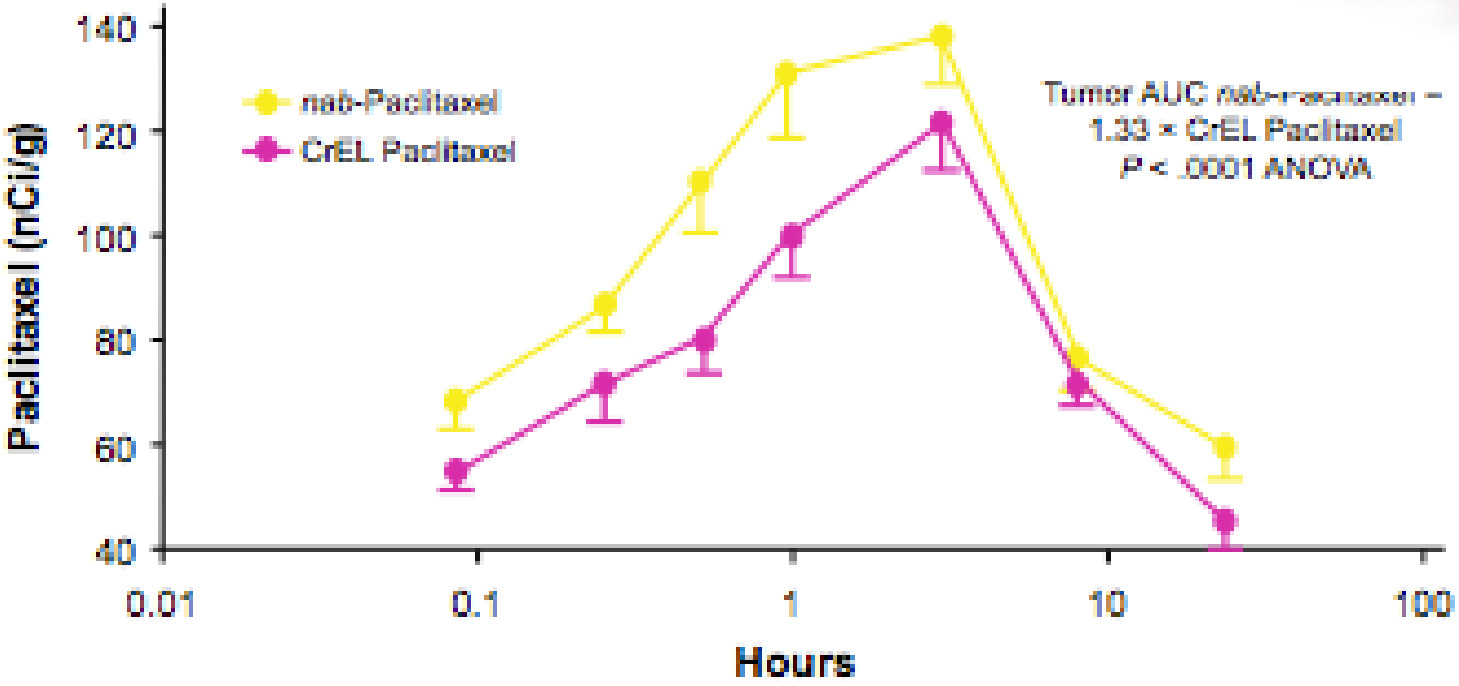
Comparative tissue distribution (ratio) of radiolabeled drug in mice bearing human breast tumor xenografts 1 hour after dose[1,2].

Plus grande spécificité de distribution

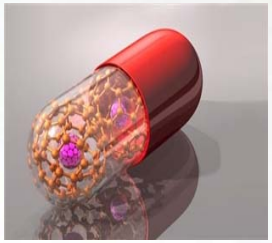
1) Hawkins M, *et al.* AACR. 2003. Poster 1189.
2) Desai N, *et al.* SPARC Expression Correlates with Tumor Response to Albumin-Bound Paclitaxel in Head and Neck Cancer Patients. *Translational Oncology.* 2009;2:59-64.7.



Nab-paclitaxel (Abraxane®)



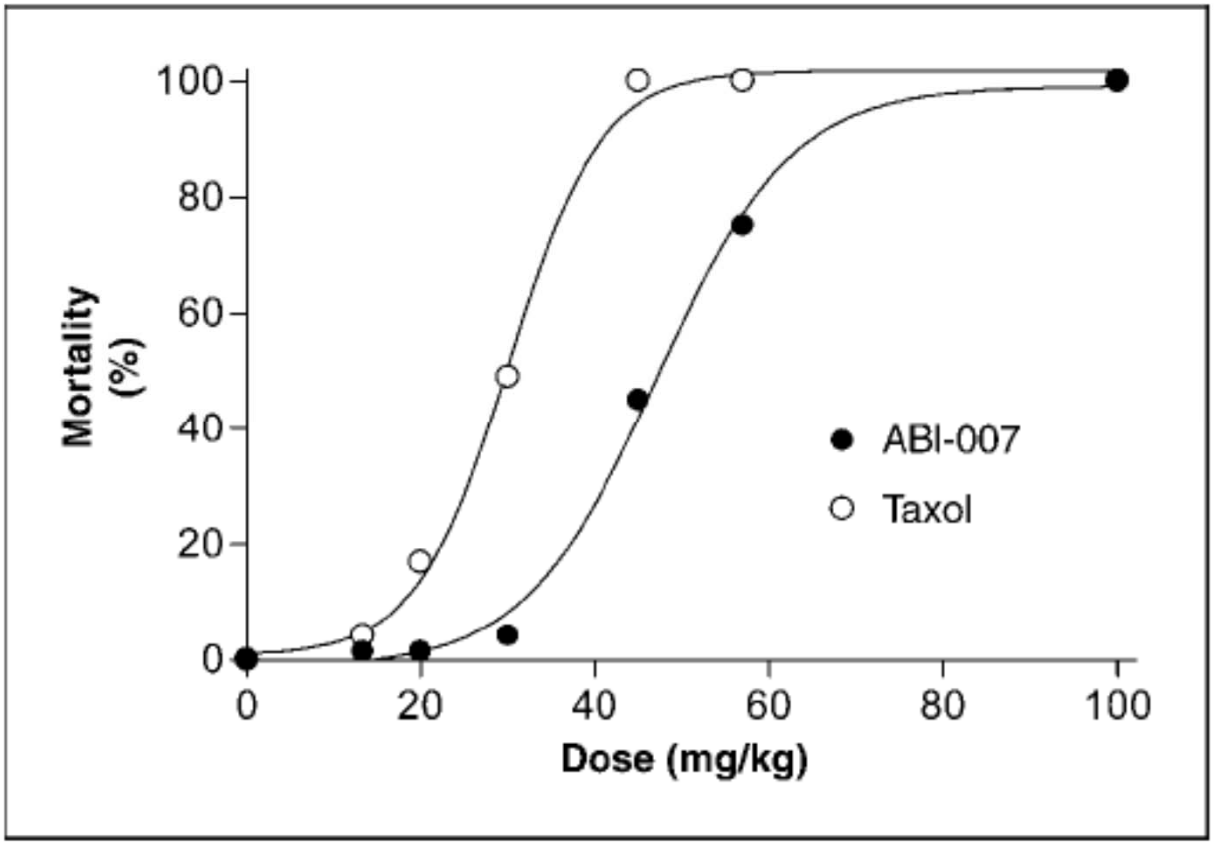
+ 30% concentration intratumorale en drogue
après administration de Nab-paclitaxel



Nab-paclitaxel (Abraxane®)

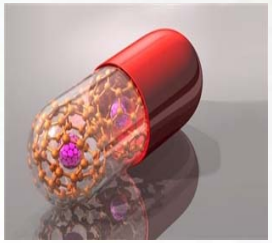
Safety

LD_{50} for Cremophor-based paclitaxel & ABI-007.
Mortality data from all tumor models as well as from non-tumor-bearing animals were lotted versus dose and curve-fitted using the Boltmann sigmoidal equation.
ABI-007 was significantly less toxic than Cremophor-based paclitaxel. p=0.017 (ANCOVA)



Meilleure tolérance: DL50: 30 *vs* 50 mg/kg
DMT: 13.4 vs 30 mg/kg

Desai N et al. Clin Cancer Res 2006



Nab-paclitaxel (Abraxane®)

Efficacité

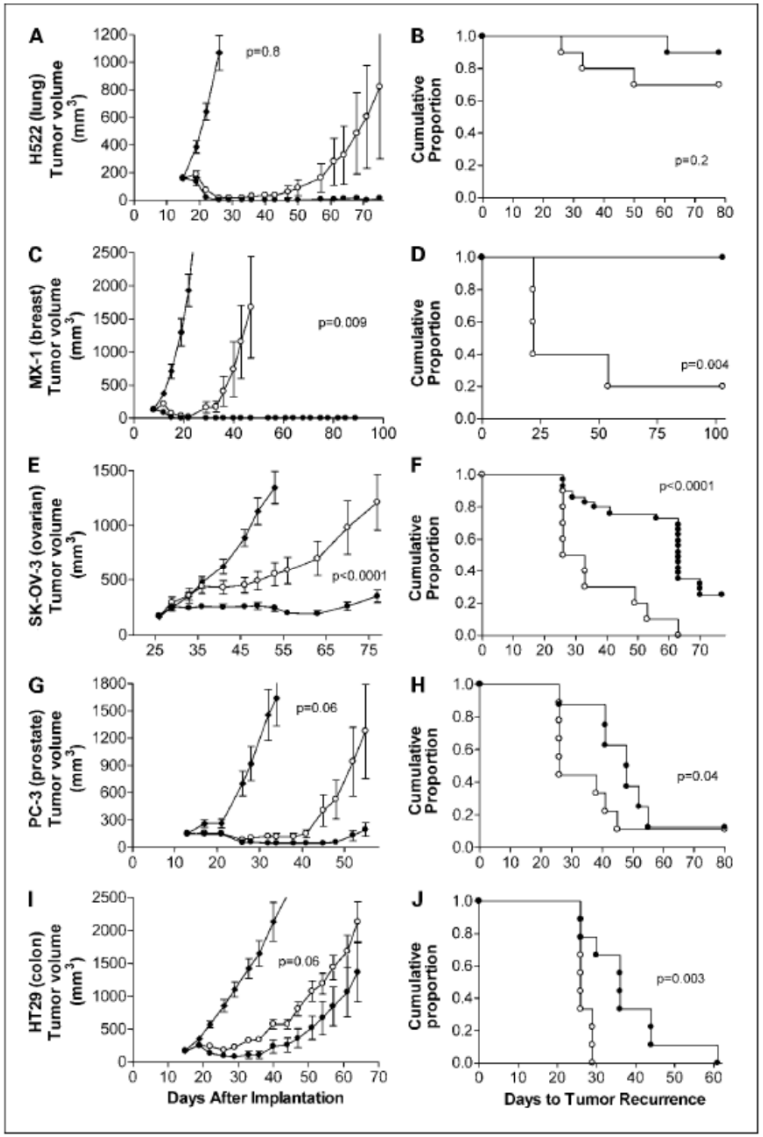
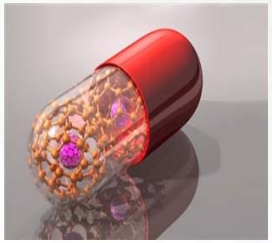


Fig. 2. Tumor volume (*A, C, E, G,* and *I*) and Kaplan-Meier analysis of tumor recurrence (*B, D, F, H,* and *J*) in five tumor xenografts treated with equitoxic doses of ABI-007 (30 mg/kg/d, ●) or Cremophor-based paclitaxel (13.4 mg/kg/d, ○). ♦, untreated controls. *A* and *B*, H522 (lung tumor xenograft); *C* and *D*, MX-1 (breast tumor xenograft); *E* and *F*, SK-OV-3 (ovarian tumor xenograft); *G* and *H*, PC-3 (prostate tumor xenograft); *I* and *J*, HT29 (colon tumor xenograft).

Efficacité optimisée!

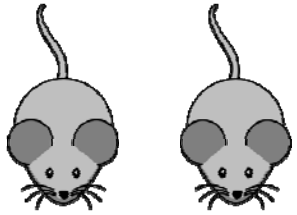
Desai N et al. Clin Cancer Res 2006

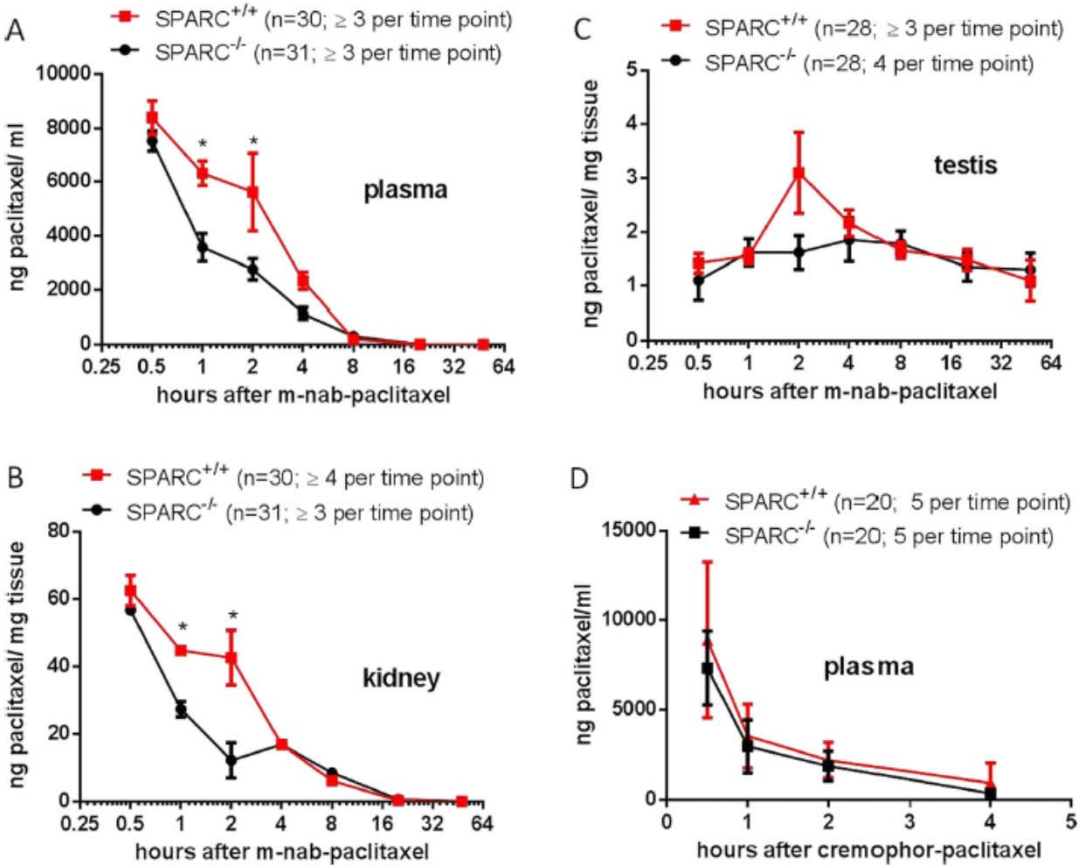


PK : Nab-drugs

SPARC

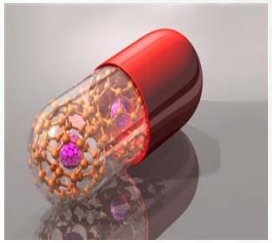
SPARC + SPARC-





L'expression de SPARC modifie la PK!

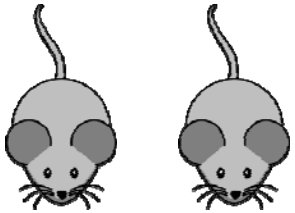
Neese et al. Gut 2013

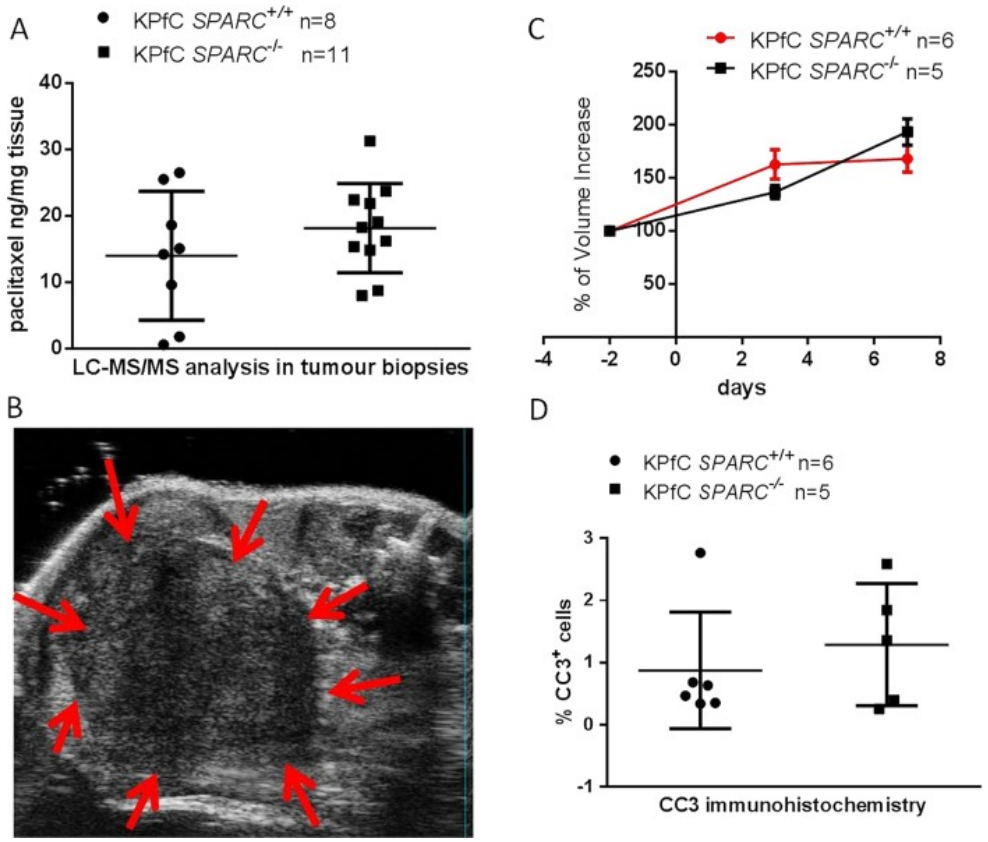


PK : Nab-drugs

SPARC

SPARC + SPARC -



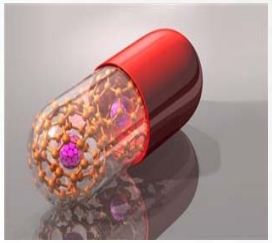


EPR Effect?

L'expression de SPARC modifie la PK

… mais est non-obligatoire pour obtenir un effet antiprolifératif !

Neese et al. Gut 2013



Nab-paclitaxel (Abraxane®)

Synergie d'action avec la gemcitabine

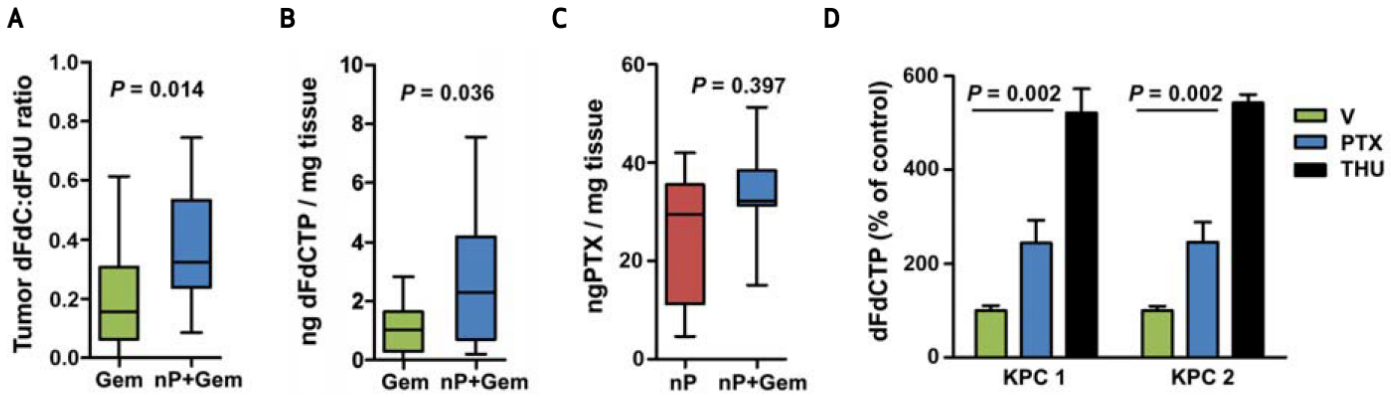
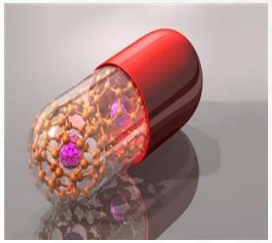


Figure 3. *nab*-Paclitaxel promotes elevated intratumoral gemcitabine levels. **A,** 2′,2′-difluorodeoxcytidine:2′,2′-difluorodeoxyuridine (dfdC:dFdU) ratio in bulk tumor was quantified in mice 2 hours after the last dose of gemcitabine. ($n \geq 12$). **B,** intratumoral levels of dFdCTP were measured in duplicate samples from mice in each cohort 2 hours after the last dose of gemcitabine. ($n \geq 12$) **C,** intratumoral levels of paclitaxel were measured in samples from mice in each cohort 4 hours after the last dose of *nab*-paclitaxel ($n \geq 7$). **D,** 2 KPC cell lines were pretreated with 10 μmol/L paclitaxel or dimethyl sulfoxide for 36 hours or 10 μmol/L tetrahydrouridine (THU; cytidine deaminase inhibitor) for 30 minutes as a positive control and incubated with 1 μmol/L gemcitabine for 2 hours. Levels of dFdCTP were then measured. Data are representative of 3 independent experiments. G, gemcitabine; nP + G, *nab*-paclitaxel and gemcitabine.

Le nab-paclitaxel accroît la quantité de gemcitabine intratumorale et favorise son activation!

Frese KK et al. Cancer Discovery 2012



Nab-paclitaxel (Abraxane®)

Synergie d'action avec la gemcitabine

Curr Pharm Des. 2012;18(19):2811-29.
Molecular targets of gemcitabine action: rationale for development of novel drugs and drug combinations.
Elnaggar M[1], Giovannetti E, Peters GJ.

RESEARCH ARTICLE

***nab*-Paclitaxel Potentiates Gemcitabine Activity by Reducing Cytidine Deaminase Levels in a Mouse Model of Pancreatic Cancer**

Kristopher K. Frese[1], Albrecht Neesse[1,3], Natalie Cook[1,2], Tashinga E. Bapiro[1,2], M
Duncan I. Jodrell[1,2], and David A. Tuveson[1,2]

AUTHOR'S VIEW

Oncolmmunology 2:12, e27231; December 2013; © 2013 Landes Bioscience

Macrophages increase the resistance of pancreatic adenocarcinoma cells to gemcitabine by upregulating cytidine deaminase

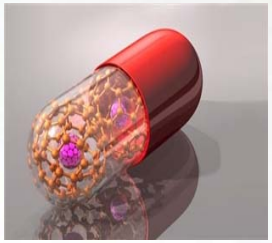
Moran Amit and Ziv Gil*

The Laboratory for Applied Cancer Research; Department of Otolaryngology Head and Neck Surgery; Rambam Medical Center; the Technion Israel Institute of Technology; Haifa, Israel

Keywords: pancreatic ductal adenocarcinoma, chemotherapy, gemcitabine, resistance, macrophages, cytidine deaminase

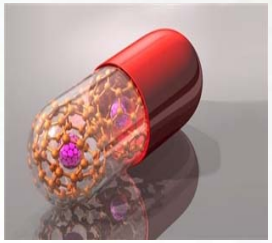
Le nab-paclitaxel module la cytidine deaminase (CDA) tumorale, une cause majeure de résistance au Gemzar!

Frese KK et al. Cancer Discovery 2012



Intérêts du Nab-paclitaxel, Abraxane®

- PK optimisée: PK linéaire, phase de distribution,1/2 vie plus longue, diminution des temps de perfusion …
- Meilleure Tolérance: Ø Cremophore, spécificité tumorale
- Meilleure Efficacité: Augmentation des doses, spécificité tumorale et MET



Merci de votre attention!