

***How Does the Human Body Handle  
NanoPharmaceuticals?***

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# **Nanoparticle**

## **Drug Delivery Systems**

- 1. PK/PD issues**
- 2. Protein Delivery**
- 3. Blood-Brain Barrier (BBB) Drug Transport**
- 4. Abraxane (albumin-bound paclitaxel)**

# FDA Approved Nanoparticle DDS (partial list)

Drug (Trade name)	Indication (s)
Liposomal amphotercin (Ambisome®, Ablecet®, Amphotec®)	Fungal Infections, Leishmaniasis
PEG_adenosine deaminase (Pegademase®)	Severe combined immunodeficiency,
Lyposomal cytosine arabinoside (DepoCyst®)	
Interleukin 2-diphtheria toxin fusion protein (Denileiken® , Diffitox®)	Cutaneous T cell lymphoma
Protein-bound paclitaxel (Abraxane®)	Metastatic breast cancer
Pemetrexed (Alimta®)	Malignant pleural mesothelioma

# Problems with Liposomal Particles

## 1. Rapid Uptake into/by:

- a. Liver
- b. Spleen
- c. Kidneys
- d. Reticuloendothelial System

# Effects of Protein Pegylation

**1. Size and Molecular Weight Increases**

**2. Physicochemical Alterations**

**a. Conformation**

**b. Steric Hindrance**

- **Affinity Issues**

**c. Electrostatic Binding**





**d. Hydrophobicity**

**e. pI**

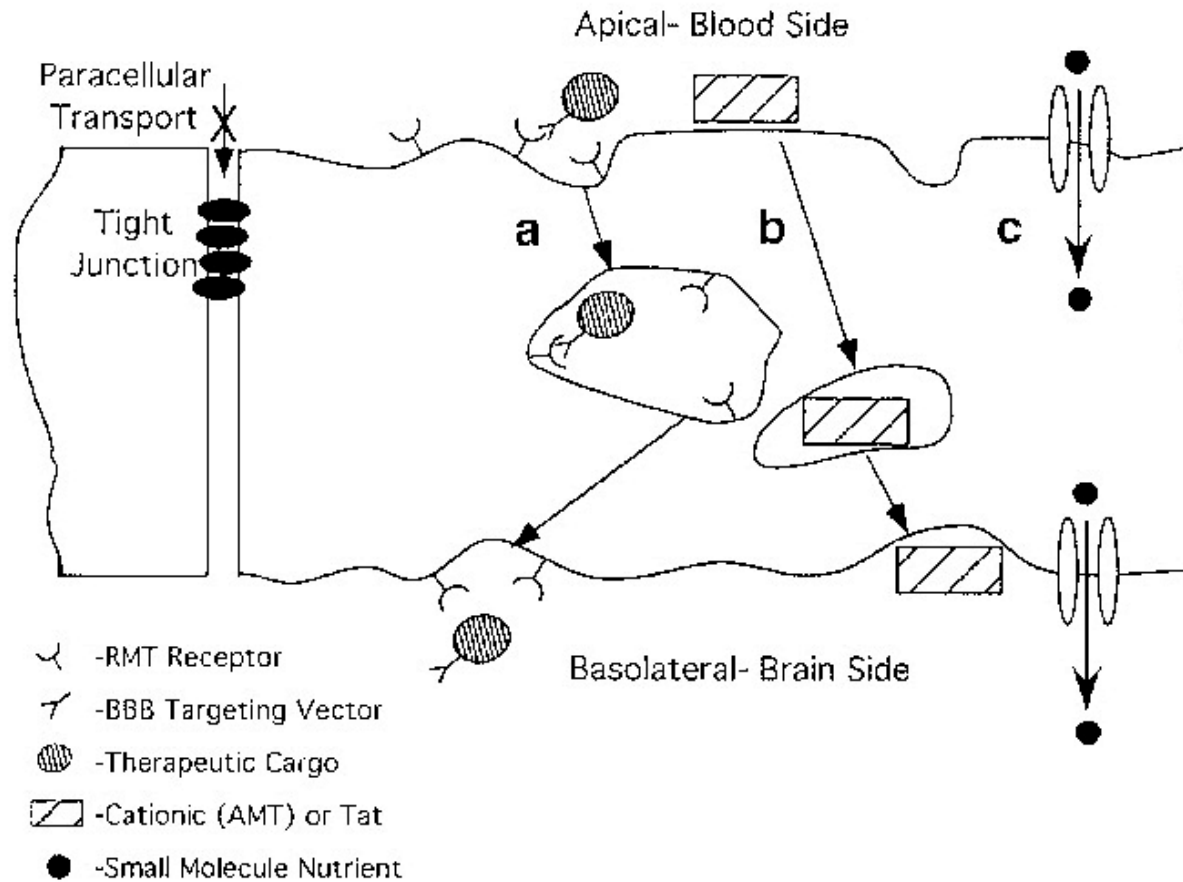
# PK/PD Consequences of Pegylation

1. Decreases in Systemic Clearance
  - a. Decrease in renal clearance ( > 40 kDa)
  - b. Proteolysis
  - c. Opsonization (macrophage uptake)

# Effect of Pegylation on PK/PD of Proteins

Pharmacokinetic Effects	Pharmacodynamic Effects
<b>Interferon-<math>\alpha</math>-2a</b> - t <sub>1/2</sub> (absorption)  20-fold	Antiviral activity (in-vitro)  12 -135 fold
- Clearance  100-fold	Antitumor Activity  18-fold
	Improved Chronic Hepatitis C treatment

# BBB Drug Transport





# Doxorubicin-loaded Nanoparticles

[Steiniger et al, Int. J. Cancer., 109, 759-767, 2004]

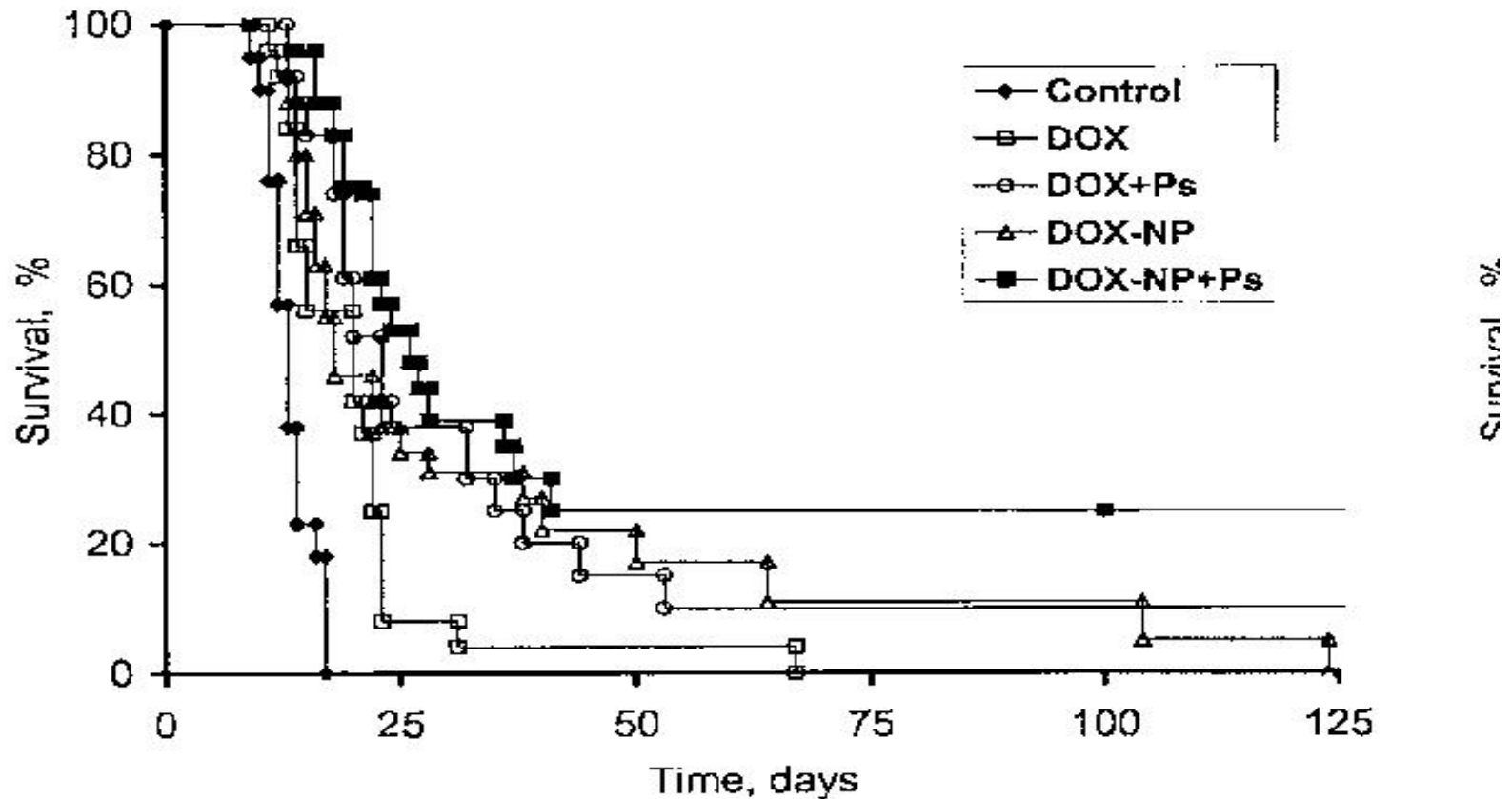
Polysorbate 80-coated poly  
(butylcyanoacrylate) doxorubicin  
nanoparticles

**Mean diameter ( $\pm$  SD):  $270 \pm 20$  nm**

**Nanoparticle content in suspension : 70%**

# Doxorubicin-loaded Nanoparticles

[Steiniger et al, Int. J. Cancer., 109, 759-767, 2004]



## Nociceptive Threshold (% MPE, mean $\pm$ SD) after i.v. injection of dalargin-loaded polysorbate 80 and apolipoprotein-coated PBCA nanoparticles in mice

Apolipoprotein	15 min	30 min	45 min	60 min	120 min
None (control)	35.2 $\pm$ 5.8	50.4 $\pm$ 4.1	49.5 $\pm$ 4.5	36.5 $\pm$ 13.7	7.10 $\pm$ 6.3
Apo B	30.9 $\pm$ 19.4	74.7 $\pm$ 15.8*	58.7 $\pm$ 8.03*	45.1 $\pm$ 18.6	25.5 $\pm$ 16.4
Apo E	61.4 $\pm$ 8.59*	62.1 $\pm$ 6.91	64.5 $\pm$ 14.0	62.3 $\pm$ 11.8*	51.7 $\pm$ 12.9*
Apo All	1.98 $\pm$ 9.56	0.50 $\pm$ 10.58	12.81 $\pm$ 16.8	18.29 $\pm$ 21.81	48.8 $\pm$ 13.24*

Kreuter et al, J. Drug Targeting 10, 317-325 (2002)

# Mechanisms Involved

[Steiniger et al, Int. J. Cancer., 109 , 759-767, 2004]

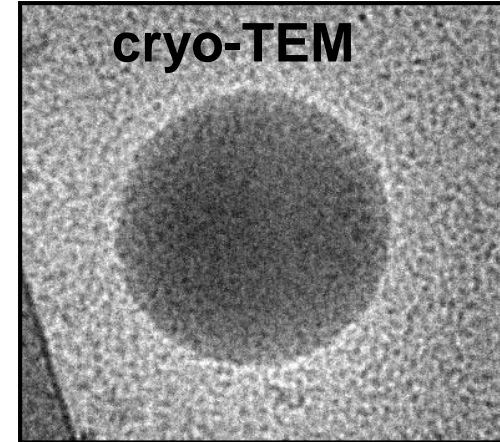
1. Endocytosis (LDL receptor mediated)
  - a. Apolipoprotein B
  - b. Apolipoprotein E

# **Abraxane versus Taxol**

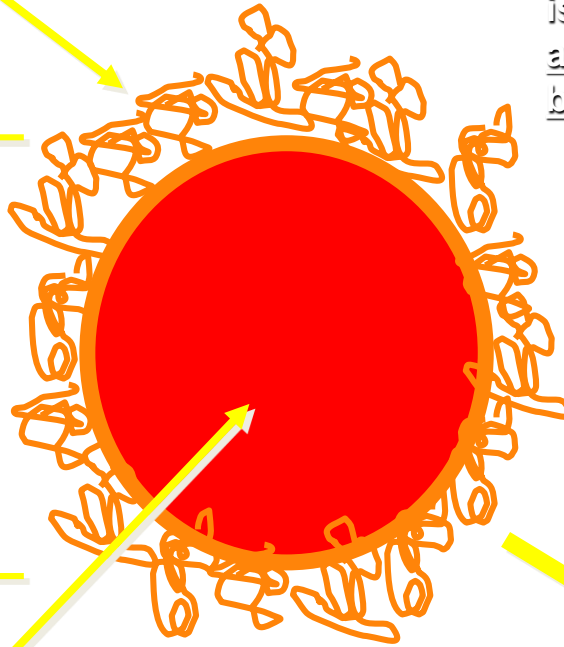
# Nanoparticle Albumin-bound (*nab*) platform technology

Albumin

Active drug in nanoparticle is in non-crystalline, amorphous, readily bioavailable state

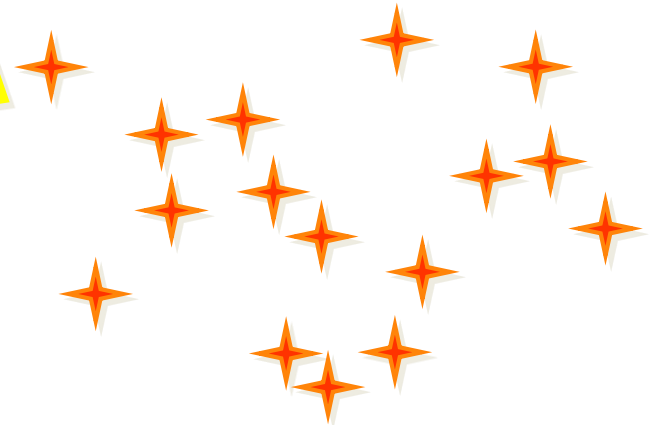


Mean size =  
50-150 nm

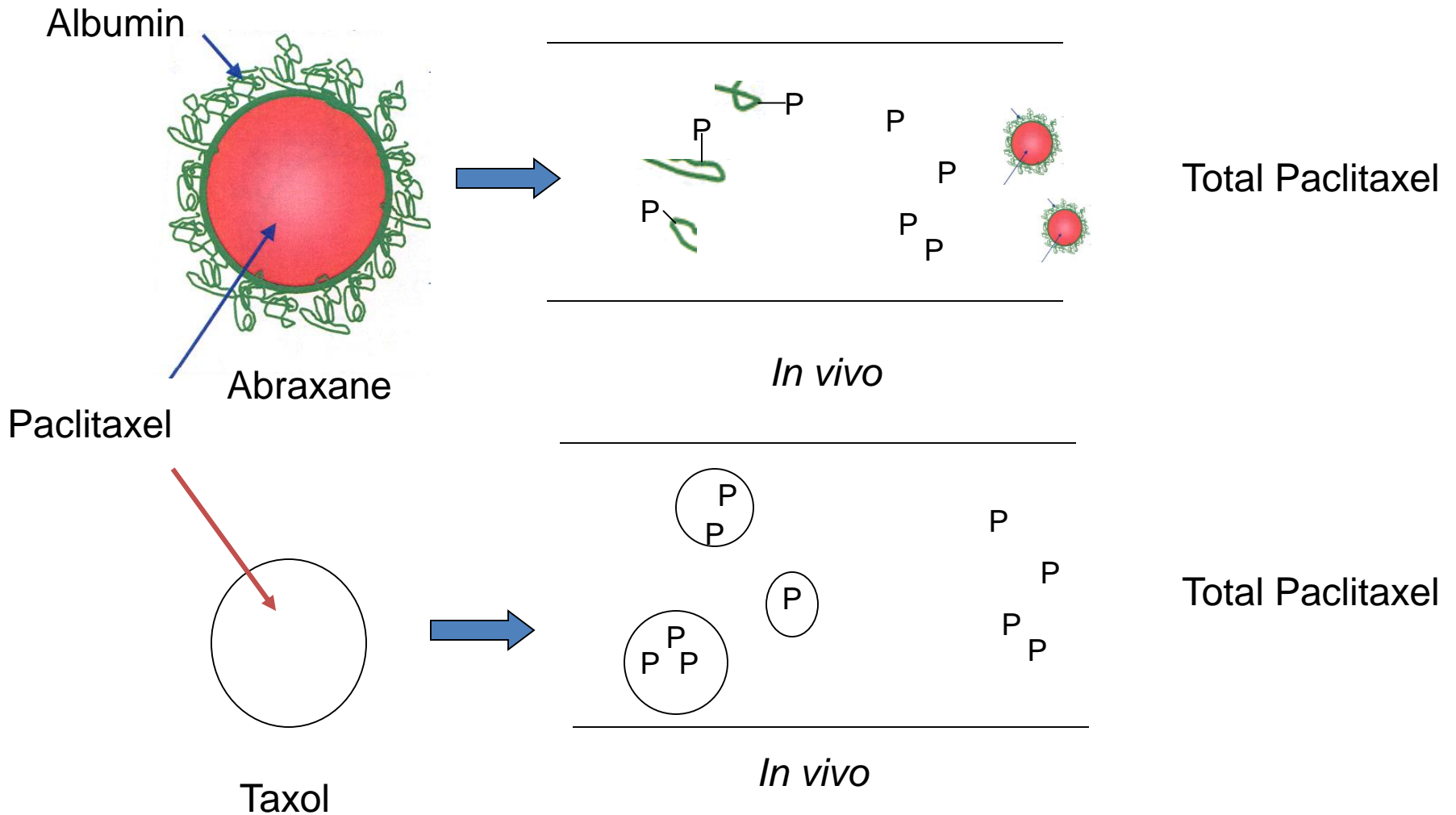


Hydrophobic drugs,  
e.g., Paclitaxel,  
docetaxel, rapamycin  
etc.

Concentration dependent  
dissociation into  
individual drug-bound  
albumin molecules



# PK Comparison- Paclitaxel moieties (Bioscience Website)



# Abraxane versus Taxol

## (3 week treatment)

Drug	Dose (mg)	Tumor Size	Tumor in "check" (weeks)	NP (%)	Neuropathy # of patients)
Abraxane (130 nm)	260 (30 min)	33% ↓	21.9	34	24
Taxol *	175 (3 hr)	19% ↓	16.1	54	5

\* : dissolved in Cremophor      NP= neutropenia



# Conclusions

- **Nanoparticle DDS offers innovative approaches to drug targeting and delivery**
- **The field is an evolving area**