

***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

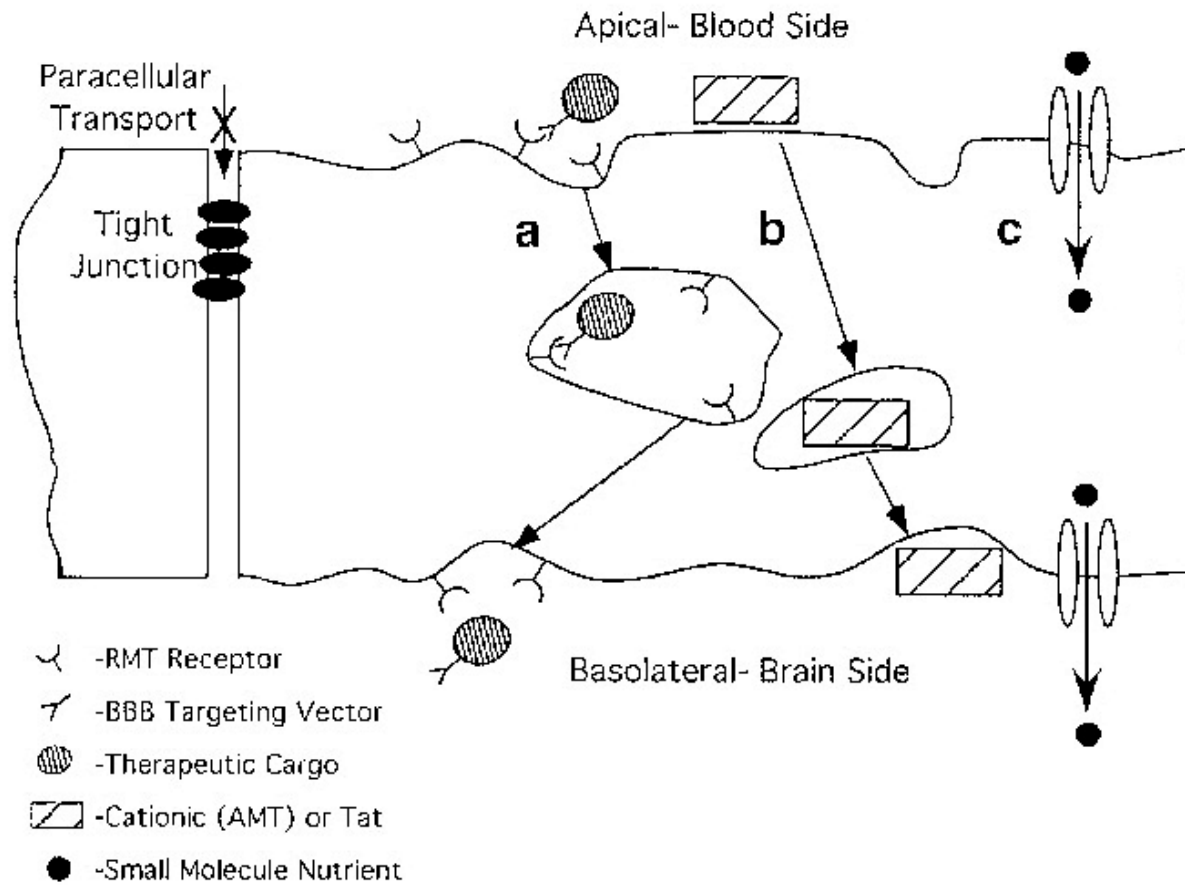
PK/PD Consequences of Pegylation

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
Interferon-α-2a - t _{1/2} (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]

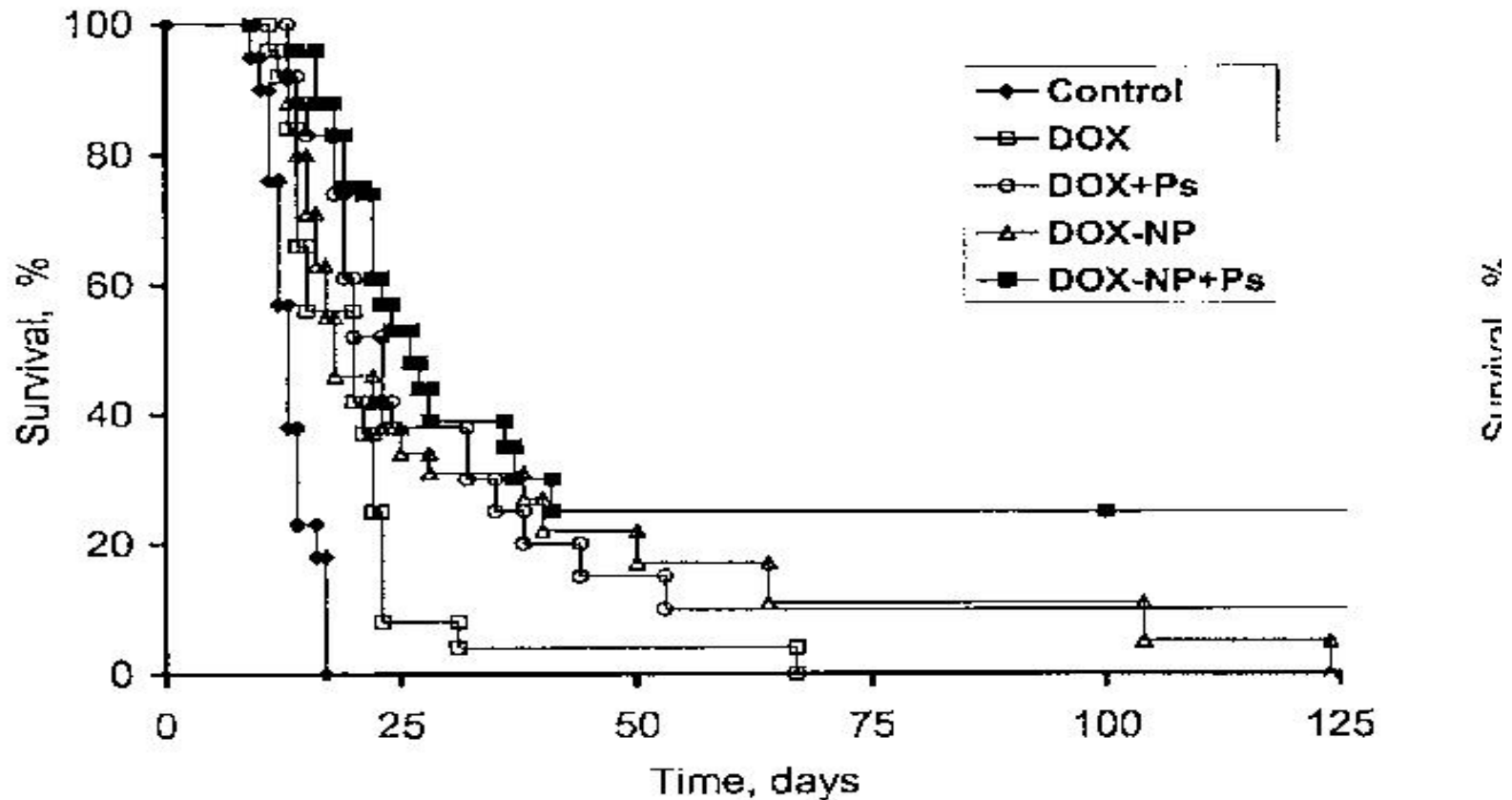
Polysorbate 80-coated poly
(butylcyanoacrylate) doxorubicin
nanoparticles

Mean diameter (\pm SD): 270 ± 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]

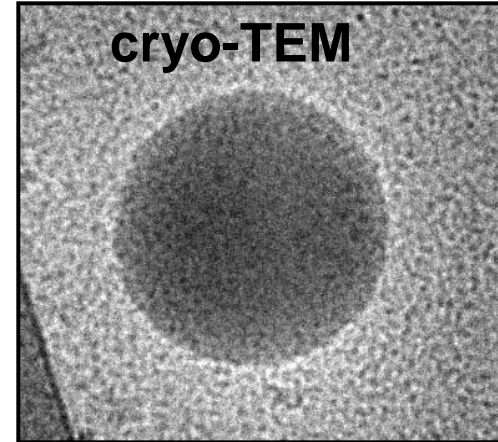
1. Endocytosis (LDL receptor mediated)
 - a. Apolipoprotein B
 - b. Apolipoprotein E

Abraxane versus Taxol

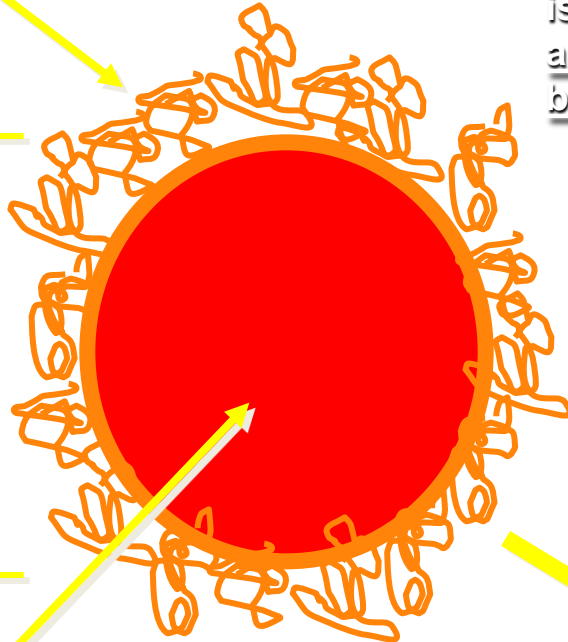
Nanoparticle Albumin-bound (*nab*) platform technology

Albumin

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

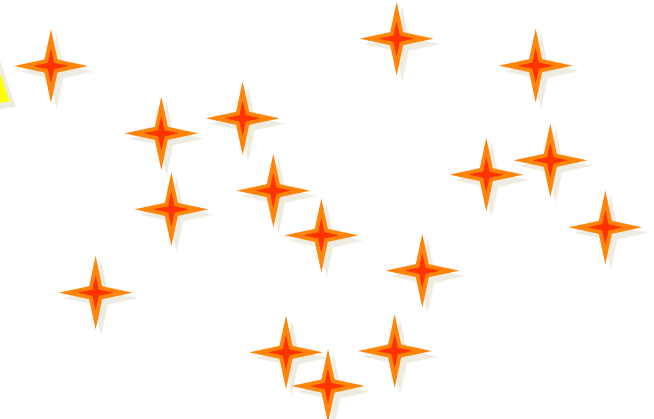


Mean size =
50-150 nm

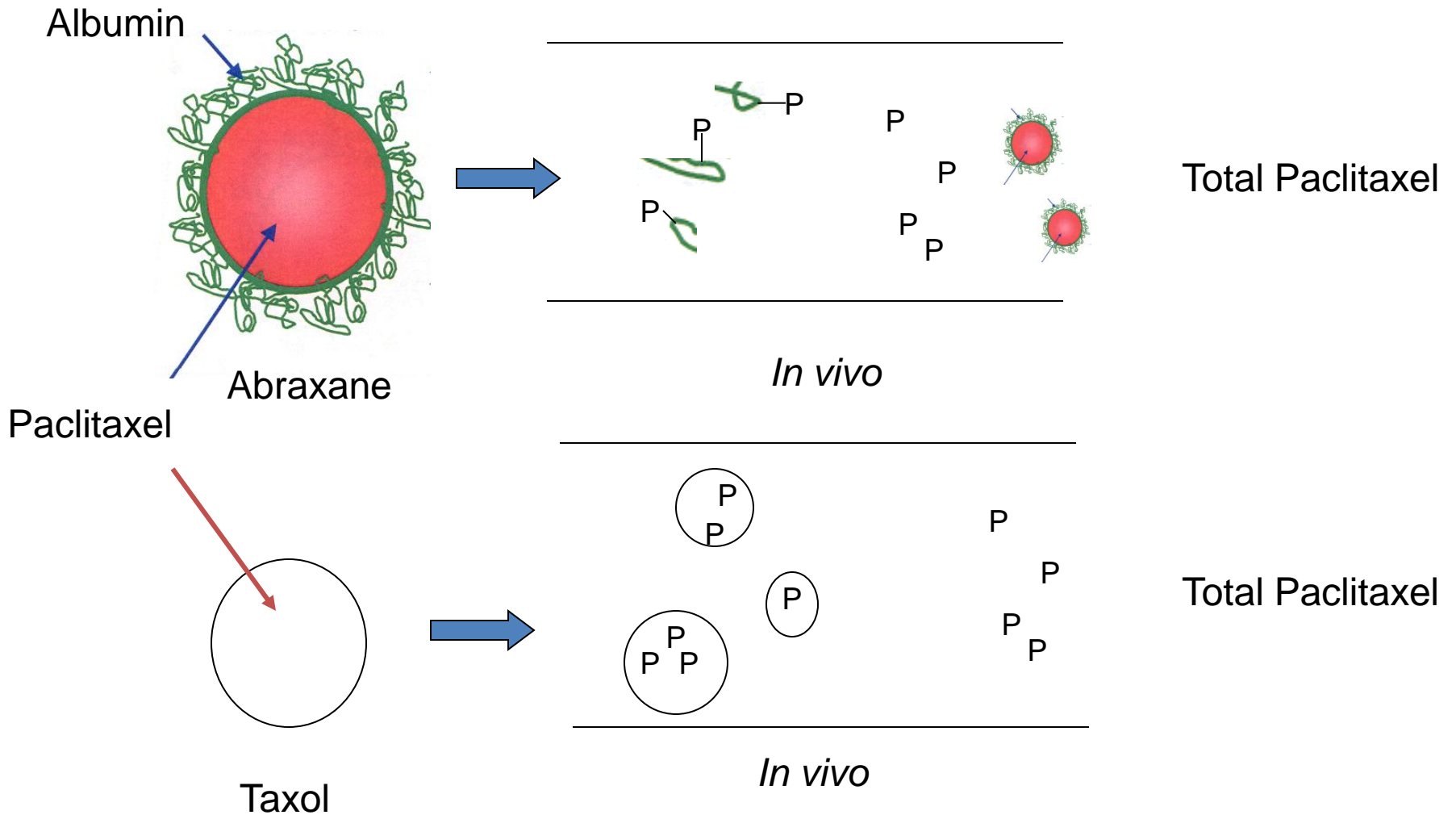


Hydrophobic drugs,
e.g., Paclitaxel,
docetaxel, rapamycin
etc.

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**