How Does the Human Body Handle NanoPharmaceuticals?

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Why NanoPharmaceuticals?

- More Effective (enhanced target delivery tumor)
- Less Toxic
- Combat Generics

FDA Approved Nanoparticle Drug Delivery Systems (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

NanoPharmaceuticals - Schematics

Polymer Micelle

Unilamellar Vesicle

Polymeric Nanosphere





FACTORS AFFECTING NANOPARTICLE DISPOSITION

- SIZE
- SHAPE (geometry)
- SURFACE PROPERTIES (charge)

Liposomal Drug Delivery Systems

Problems with Liposomal Particles

Rapid Uptake into/by:

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

Liposome-Based Nanopharmaceuticals Doxorubicin

Myocet[®] Doxil[®]

Liposome

PEGylated liposome





Myocet[®]

- Doxorubin key drug to treat breast cancer
- Liposomal form of doxorubin complexed with citrate inside the vesicle
- Release controlled by drug aggregation and pH

Doxorubicin Pharmacokinetics



Mean (\pm SEM) plasma concentrations versus time for doxorubicin and doxorubicinol in patients receiving TLC D-99 (A) or conventional doxorubicin (B).

Swenson et al., Anti-Cancer Drugs 14:23t9-246, 2003

Doxorubicin Pharmacokinetics (cont'd)

FORMULATION	Cmax (μM)	Clearance (L*H/M2)	VOL.DISTRIBUTION,ss (L)
MYOCET ®	16.0	3.05	34.2
CONVENTIONAL	1.67	27.1	851

Swenson et al., Anti-Cancer Drugs 14:239-246, 2003

Liposome-Based Nanopharmaceuticals Doxorubicin

Myocet[®] Doxil[®]

Liposome

PEGylated liposome





Doxorubicin Clearance (L*hr/M2)

Myocet®	3.05
Doxil®	0.041

BBB Drug Transport



Doxorubicin-loaded Nanoparticles [Steiniger et al, Int. J. Cancer., <u>109</u>, 759-767, 2004]

Polysorbate 80-coated poly (butylcyanoacrylate) doxorubicin nanoparticles

Mean diameter (± SD): 270 ± 20 nm Nanoparticle content in suspension : 70%

Doxorubicin-loaded Nanoparticles

[Steiniger et al, Int. J. Cancer., <u>109</u>, 759-767, 2004]



Mechanisms Involved

[Steiniger et al, Int. J. Cancer., <u>109</u>, 759-767, 2004]

Endocytosis (LDL receptor mediated)

- a. Apolipoprotein B
- **b.** Apolipoprotein E

BBB transport: Dalargin

Nociceptive Threshold (% MPE, mean ± SD) after i.v. injection of dalargin-loaded polysorbate 80 pre-coated PBCA nanoparticles (NPs) in mice

Apolipoprotein (ALP) was coated onto the surface of the pre-coated NPs

ALP	15 min	30 min	45 min	60 min	90 min
Control	35.2 ± 5.8	50.4 ± 4.1	49.5 ± 4.5	36.5 ± 13.7	7.10 ± 6.3
Аро В	30.9 ± 19.4	74.7 ± 15.8*	58.7 ± 8.03*	45.1 ± 18.6	25.5 ±16.4
Аро Е	61.4 ± 8.59*	62.1 ± 6.91	64.5 ± 14.0	62.3 ± 11.8*	51.7 ± 12.9*
Apo All	1.98 ± 9.56	0.50 ± 10.58	12.81 ± 16.8	18.29 ± 21.81	48.8 ±13.24*

*p < 0.05

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

Abraxane versus Taxol

http://www.youtube.com/watch?v=OmRzyqc6QrA

Nanoparticle Albumin-bound (*nab*) platform technology



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					

FDA

- "Taxol has a higher incidence of neutropenia and hypersensitivity reactions"
- "Abraxane has a higher incidence of peripheral neuropathy, nausea, vomiting, diarrhea and asthenia"



"FDA Agrees that in the metastatic breast cancer study Abraxane had a higher tumor response rate than Taxol"

Conclusions

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

Carbon Aerogel World's Lightest Material



"... a quantity of aerogel equal in volume to a typical human body would weigh only ... 1/40th of a pound."

http://www.huffingtonpost.com/2013/04/02/lightest-material-earth-carbon-aerogel_n_2980978.html

QUESTIONS?