NANOMEDICINES ON THE MARKET AND IN DEVELOPMENT:

Nanoparticles

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

2nd-3rd SEPTEMBER 2010
EUROPEAN MEDICINES AGENCY
1ST INTERNATIONAL WORKSHOP ON NANOMEDICINES

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Current positions

- *Full Professor, Faculty of Pharmacy University of Lisbon - FFUL (Portugal)*
- *Coordinator of Nanomedicine & Drug Delivery Systems research group at the Research Institute for Medicines and Pharmaceutical Sciences (iMed.UL), since 2007*
- *Member of the General Council at the University of Lisbon (Portugal), since 2008*
- *Member of the Medicines Evaluation Committee at INFARMED and different positions in European regulatory affairs (1995-2002 and since September 2008,Portugal)*
- *Member of adhoc expert group in nanomedicines at EMA (since April 2009)*
- *Member of the coordination of MSc$_s$ in Regulatory Affairs (since 2001), in Advanced Pharmacotechnics (since 2006) and in Pharmaceutical Engineering (since 2007) at FFUL*
- *Doctoral Programme in BioNanotechnology (University Lisbon, approved 2009, to be started)*
- *Member of the Executive Committee of EUFEPS since 2009 (liaison with Network in Pharmacogenetics/Pharmacogenomics, chair of Network in Regulation & Science 2010, currently establishing Network in Nanomedicine)*
- *Controlled Release Society (CRS), Committee in Regulatory Affairs, since 2010*
- *Member of Board, Portuguese Society for Pharmaceutical Sciences (SPCF) since 2005*

- The views and opinions hereby expressed reflect only my personal opinion and not the views of institutions or organisations with which I'm or have been affiliated in the past or present

Technology Classes in clinical trial or the market

Liposomal - lipidic

± targeting and imaging agents

Long circulating

Long circulating targeted

Targeted

1 drug

Unilamellar liposome

2 drugs

combination therapy

Unilamellar liposome

Multilamellar liposome

lipidic drug mixtures

Polymer Conjugates

polymer-drug conjugates ± targeting/imaging agents

PEG (polymer)
-protein
-aptamer conjugates

Protein/Ab Conjugates

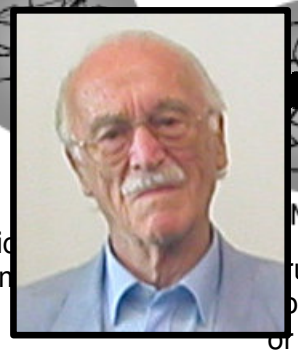
Block copolymer micelles

drug maybe entrapped or covalently bound

± targeting groups

"Nanoparticles"

nm: 5-25, 10-20, 60-200, 60-200, <1,000, 5-200, <1,000, 20-200



lipidic polym

Nanoparticle

rug non ovalently or covalent bound

metallic:- gold, silver, iron oxide (polymer coatings used to stabilise)

Long circulating

Long circulating targeted

Nanosphere

Conventional

Targeted

multilayered nanoparticle

nanocapsule, nanoshell

(NB many nanoparticles are not round)

Nano-sized drug crystals

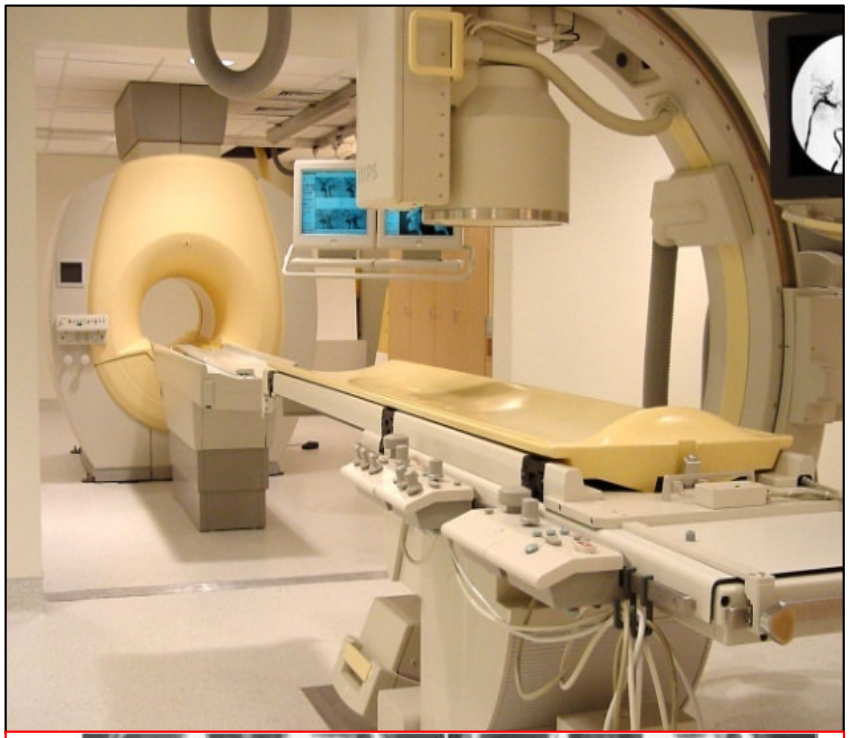
Bioactive Synthetic Polymers/Vesicles

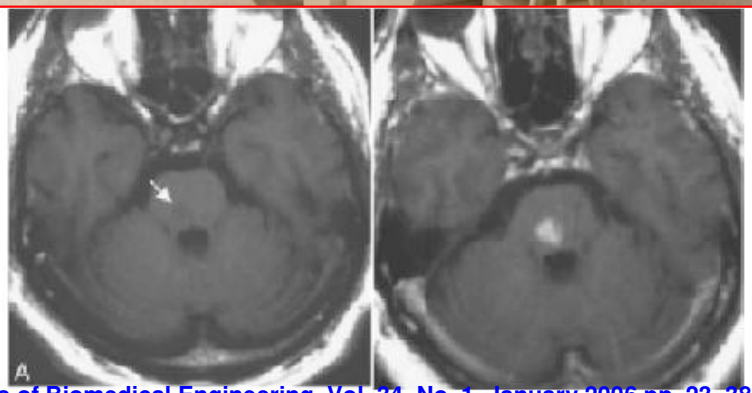
Crosslinked (Nano) Gels

Objectives

- Review the current status of medicinal products (nanopharmaceuticals)
- Review the key factors for design in respect of specific medical use
- Describe the key factors for risk-benefit assessment looking at quality, safety and efficacy
- Emerging technologies
- Specific challenges and opportunities

MRI contrast agents





Annals of Biomedical Engineering, Vol. 34, No. 1, January 2006 pp. 23–38.

Paramagnetic:

Gadopentetic acid · Gadoteric acid · Gadodiamide · Gadolinium · Gadoteridol · Mangafodipir · Gadoversetamide · Ferric ammonium citrate · Gadobenic acid · Gadobutrol · Gadoxetic acid

Superparamagnetic:

Ferumoxsil · Ferristene · Iron oxide, nanoparticles

Nanoparticulate systems:

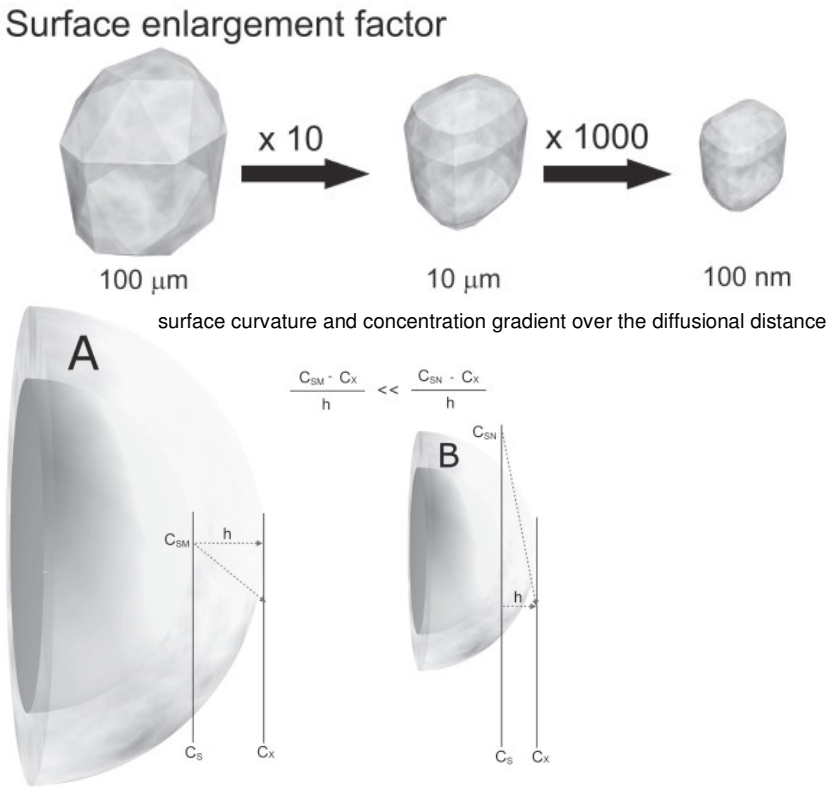
- **Iron oxide nanoparticles coated with carboxydextran (Cliavist/Resovist,Bayer Schering Pharma AG)**
- **Ultra small superparamagnetic iron oxide (USPIO) to detect metastatic disease in lymph nodes (Combidex / Sinerem, Guerbet in EU)**
- **Superparamagnetic iron oxide associated with dextran for intravenous administration as a MRI contrast medium for the detection of liver lesions that are associated with an alteration in the RES (Endorem/Feridex, Guerbet in EU)**

MR-TIP,

Magnetic Resonance -Technology Information Portal

NanoCrystal® particles

Jens-Uwe A H Junghanns and Rainer H Müller, Int J Nanomedicine. 2008 September; 3(3): 295–310.



Rapamune, (Sirolimus), Elan/Wyeth
Emend (Aprepitatnt), Elan/Merck
Tricor (Fenofibrate), Elan/Abbot
Triglide (Fenofibrate), SkyePharma/First Horizon
Megace ES® (megestrol acetate) Elan/Par Pharm. Co.

Characteristics:

- Size below 1 µm
- 100% drug, no carrier
- Generally needed to be stabilized
- Crystalline or amorphous structure
- Increase of dissolution velocity6 – Increase in saturation solubility7 – Amorphous particle state offers advantage

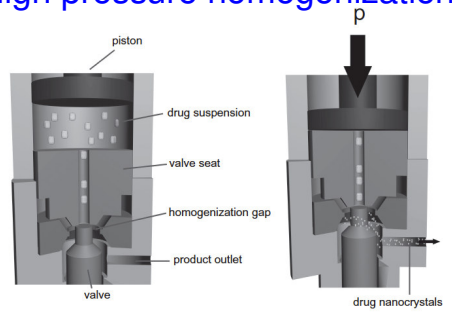
Claims:

- **Improved bioavailability, through application of the NanoCrystal® technology brings one or more practical benefits for poorly water soluble compounds:**
  - increased rate of absorption
  - reduction in required dose
  - reduction in fed/fasted variability
  - improved dose proportionality
  - smaller dosage forms
  - more convenient dosage forms
  - rapid Formulation Development
  - applicable to all routes of administration any dosage form (?)

Nanocrystals: technologies

Technologies:

High pressure homogenization



Technology	Advantages	Disadvantages
Precipitation	- finely dispersed drug - good control of desired size	- needs to be stabilized - organic solvent residue - not universally applicable, only drugs with certain properties are possible (eg, soluble in at least one solvent)
Milling	- low energy technique - proven by 4 FDA approved drugs	- residue from milling media - can be a slow process (several days) - needs to be stabilized - large batches difficult to produce due to size of milling chamber
Homogenization	- universally applicable - no problem with large batches - fast method (several minutes possibly) - water free production possible	- high energy technique - great experience needed

Jens-Uwe A H Junghanns and Rainer H Müller, Int J Nanomedicine. 2008 September; 3(3): 295–310.

NanoCrystal®: Rapamune (clinical data in EPAR)

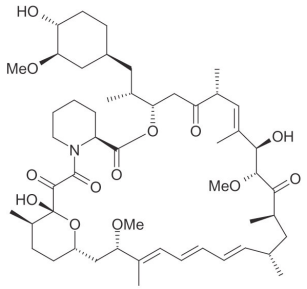
Table 6: Incidence of efficacy failure (6 and 12 months; studies 301 and 302)

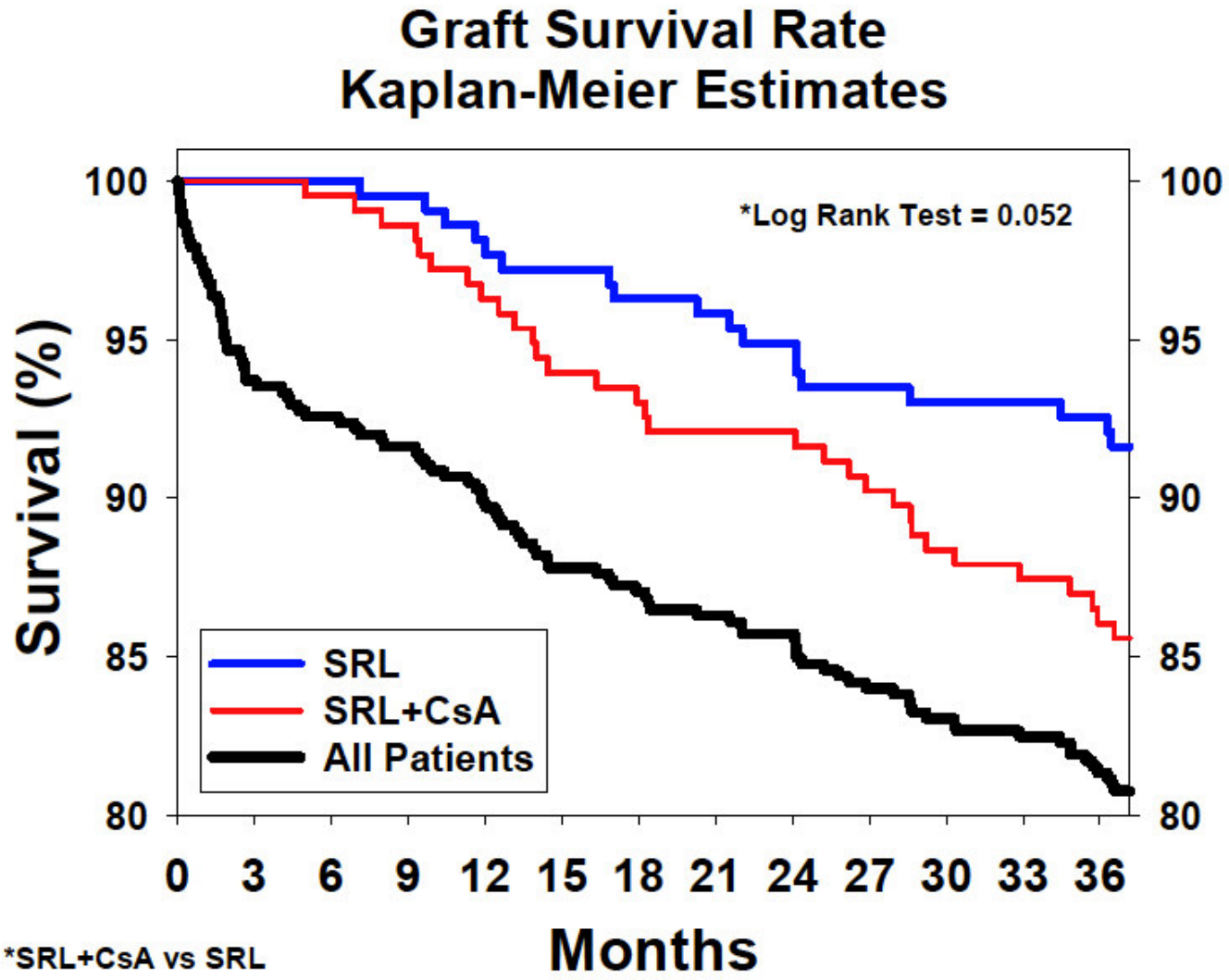
	Study 301			Study 302		
	AZA (n = 161)	SRL 2 mg (n = 284)	SRL 5 mg (n = 274)	Placebo (n = 130)	SRL 2 mg (n = 227)	SRL 5 mg (n = 219)
6 months	32.3 (52)	18.7 (53)	16.8 (46)	47.7 (62)	30.0 (68)	25.6 (56)
p-value	-	0.002	<0.001	-	0.002	<0.001

Table 7: Incidence of acute rejection (3, 6 and 12 months; studies 301 and 302)

	Study 301			Study 302		
	AZA (n = 161)	SRL 2 mg (n = 284)	SRL 5 mg (n = 274)	Placebo (n = 130)	SRL 2 mg (n = 227)	SRL 5 mg (n = 219)
3 months	29.8 (48)	15.1 (43)	8.4 (23)	40.8 (53)	22.0 (50)	18.7 (41)
p-value		0.0004	< 0.001		0.0002	< 0.001
6 months	29.8 (48)	16.9 (48)	12.0 (33)	41.5 (54)	24.7 (56)	19.2 (42)
p-value	-	0.002	<0.001	-	0.003	<0.001
12 months	31.1 (50)	21.8 (62)	14.6 (40)	43.1 (56)	26.9 (61)	23.3 (51)
p-value	-	0.046	<0.001	-	0.007	<0.001

NanoCrystal®: Rapamune (clinical in EPAR)





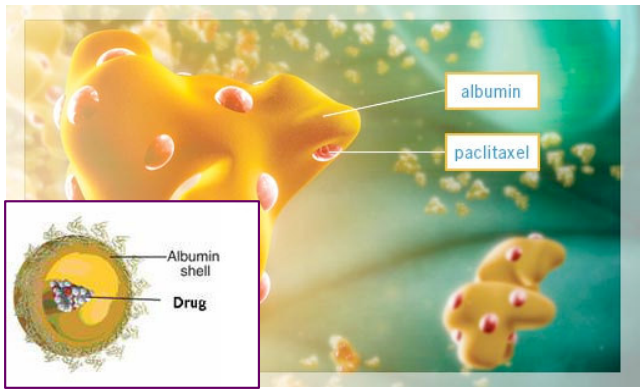
Nanocrystals: current status

TRADENAME	DRUG	INDICATION	TECHNOLOGY	COMPANY	STATUS
Rapamune®	Rapamycin	Immunosuppressive	Nanocrystal® Elan	Wyeth	Marketed
Emend®	Aprepitant	Anti-emetic	Nanocrystal® Elan	Merck	Marketed
Tricor®	Fenofibrate	Hypercholesterolemia	Nanocrystal® Elan	Abbott	Marketed
Megace ES®	Megestrol	Anti-anoretic	Nanocrystal® Elan	Par Pharm.Co.	Marketed
Triglide®	Fenofibrate	Hypercholesterolemia	IDD-P® Skyepharma	Sciele Pharma Inc.	Marketed
Semapimod®	Guanylhydrazone	TNF-α inhibitor	own	Cytokine Pharmasciences	Phase II
Paxceed®	Paclitaxel	Anti-inflammatory	unknown	Angiotech	Phase III
Theralux®	Thymectacin	Anti-cancer	Nanocrystal® Elan	Celmed	Phase II
Nucryst®	Silver	Anti- bacterial	own	Nucryst Pharm.	Phase II

Albumin nanoparticles (Abraxane®)

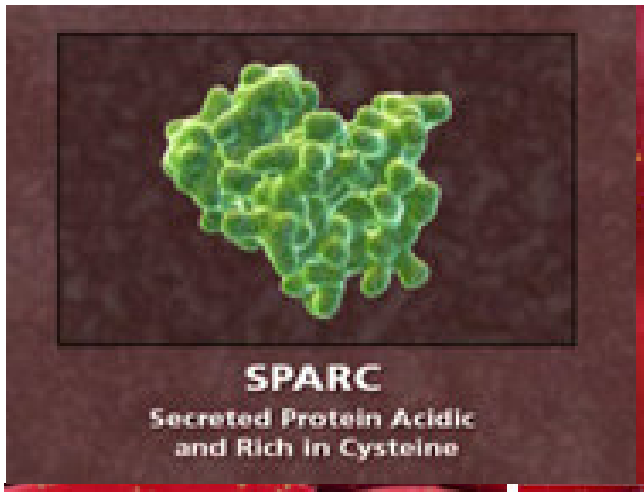
- Nanoparticle albumin-bound paclitaxel (*nab*™-paclitaxel; ABI-007; Abraxane®) is a novel CrEL-free formulation of paclitaxel.
- Prepared by high-pressure homogenization of paclitaxel in the presence of serum albumin, resulting in a nanoparticle colloidal suspension.
- Albumin concentration is 3-4%, which is similar to the albumin concentration in the blood.
- Human albumin-stabilized paclitaxel particles have an average size of approximately 130 nm, which allows intravenous infusion without the risk of capillary blockage.
- *Nab*-paclitaxel can be reconstituted in normal saline at concentrations of 2-10 mg/ml compared with 0.3-1.2 mg/ml for CrEL-paclitaxel; therefore, the volume and infusion time are reduced.
- The *nab*-paclitaxel formulation provides several practical advantages over CrEL-paclitaxel:
  - premedications for hypersensitivity reactions are not required,
  - the infusion time is shorter (30 min for *nab*-paclitaxel vs 3 h for CrEL-paclitaxel)
  - and conventional infusion equipment may safely be used

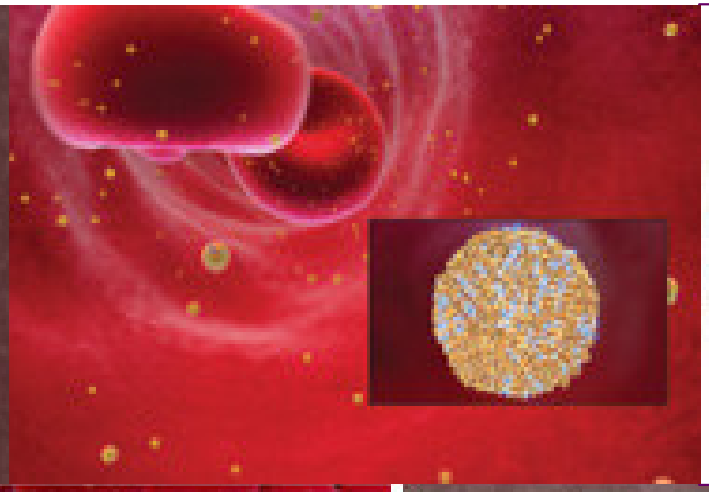
  since there is no danger of leaching plasticizers from infusion bags or tubing.

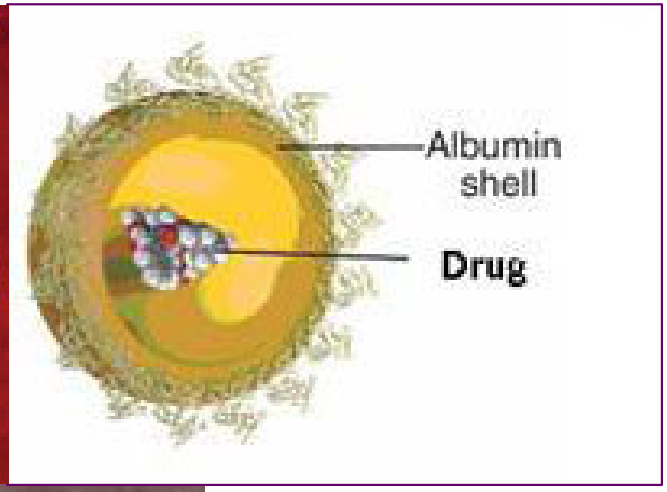


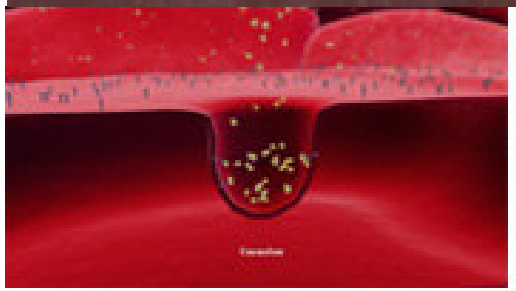
Thomas E Stinchcombe
Nanoparticle Albumin-bound Paclitaxel: a Novel Cremphor-EL®-free Formulation of Paclitaxel.
Nanomedicine. 2007;2(4):415-423

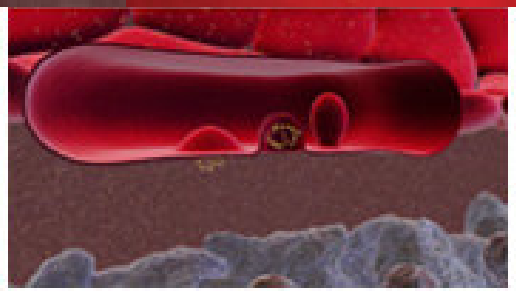
Abraxane®







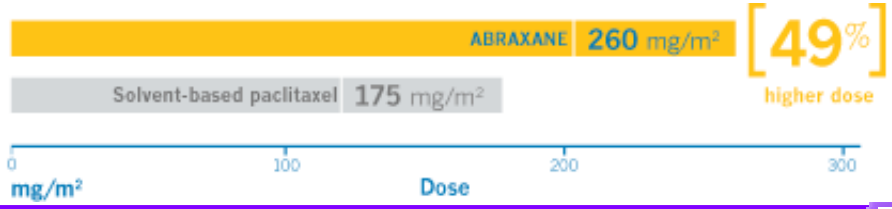




Albumin binds to caveolin-1 receptors and causes the formation of caveolae, to transport albumin across the endothelial membrane

Transcytosis is the transport of albumin across the endothelial barrier from within the blood vessel to the tumor's interstitium

SPARC is then secreted by the tumor to attract and retain albumin-bound nutrients within the tumor cell



Abraxane®: clinical

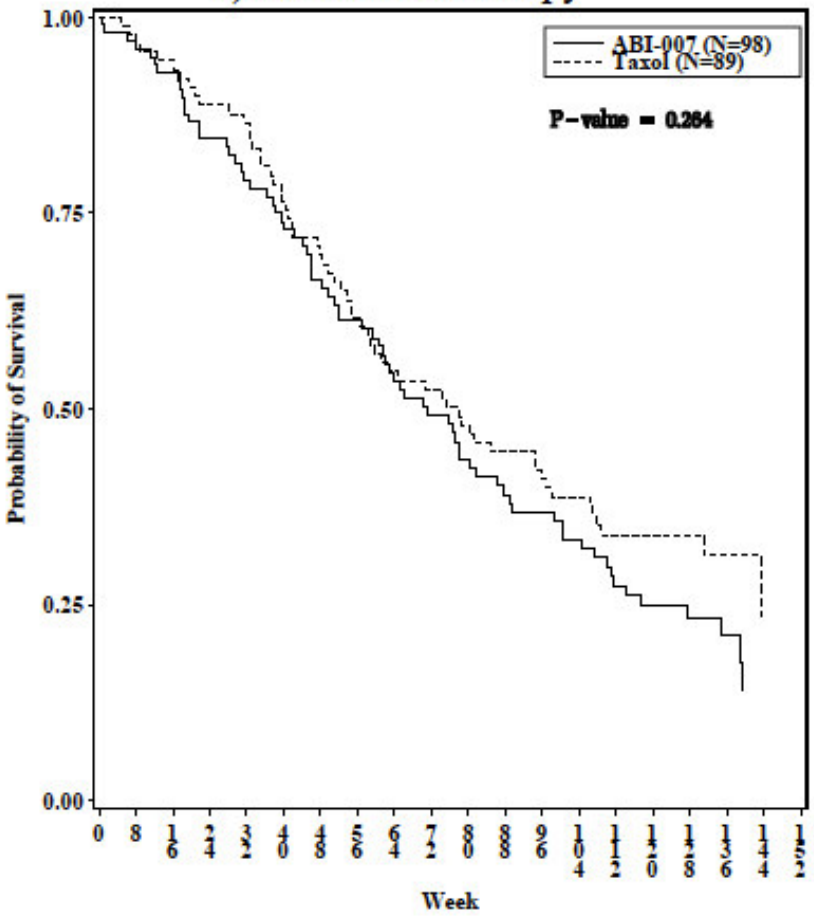
Table 10: Mean pharmacokinetic parameters

	Dose Abraxane mg/m^2	No subjects	C_{max} ng/ml (range)	Vd l/m^2 (range)	AUC_{inf} ng·hr/ml (range)	T ½ hr (range)	CLt l/hr/m^2 (range)
DM97-123	200	3	7757 (6110-10900)	401 (186-656)	8998 (7073-10536)	13.2 (4.6-21.3)	22.9 (19.0-28.4)
	300	5	13520 (11800-14200)	387 (267-524)	16736 (11530-21749)	14.4 (13.1-18.1)	18.7 (13.8-26)
CA 005-0	200	2	13400 (12700-14100)	483 (396-570)	11363 (10042-12683)	18.62 (17.4-19.84)	17.9 (15.8-19.9)
CA 008-0	260	14	22969 (4060-86700)	230.7* (53.2-493)*	14789 (5982-28680)	21.6 (16.5-29.6)	21.13 (8.72-43.4)
CA 012-0	260	12	18741 (8787-24938)	632 195.5* (348-1831)	17940 (11205-23900)	27.4 (19.8-54.7)	15.2 (10.9-23.2)

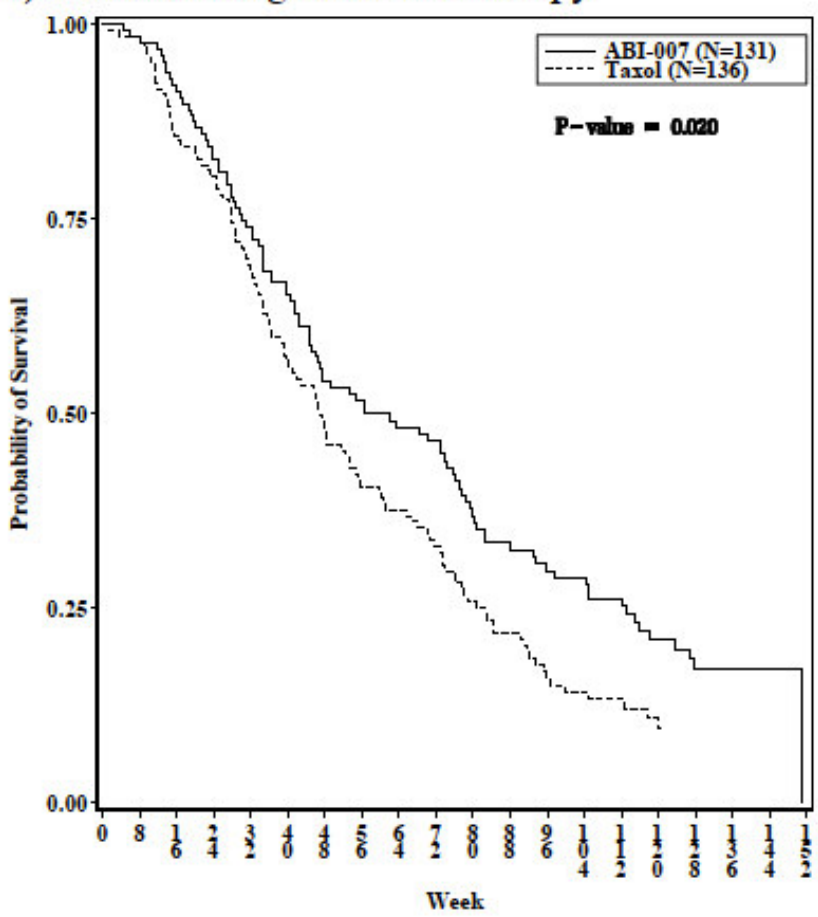
*Vdss

Abraxane®: clinical

a) In first-line therapy

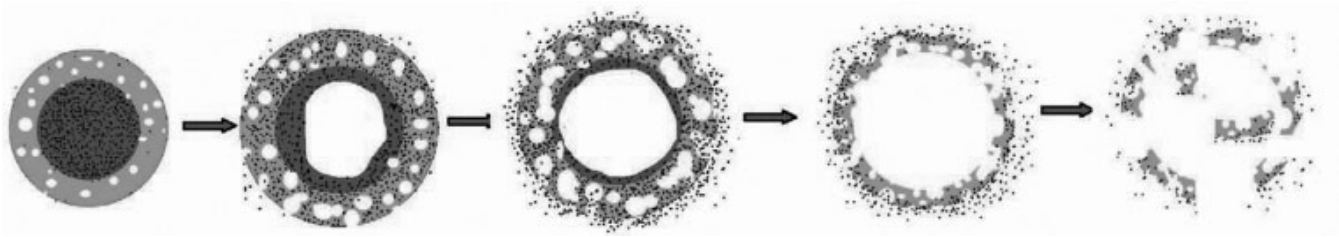


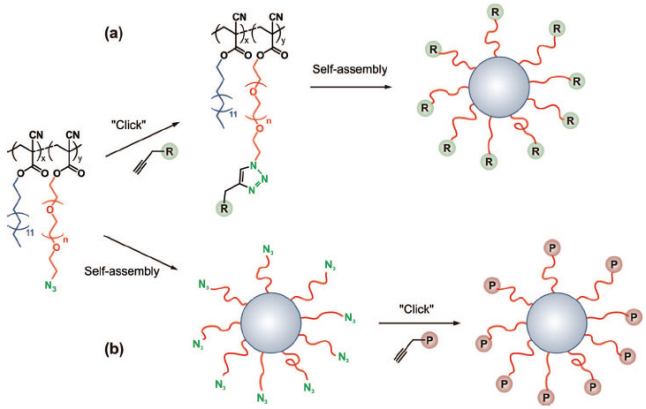
b) In second or greater line therapy



Polymeric nanoparticles

Proposed release mechanism as per F. MOHAMED, C. F. VAN DER WALLE, Journal of Pharmaceutical Sciences, Vol. 97, 71–87 (2008)



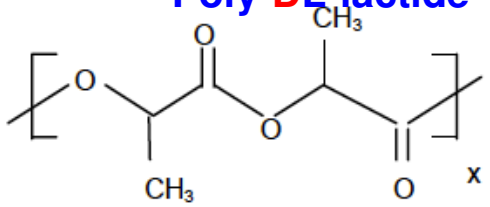


Nicolas et al, *Macromolecules, Vol. 41, No. 22, 2008*

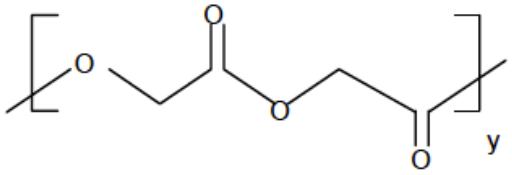
FEBS Lett. 1977 Dec 15;84(2):323-6.
Nanocapsules: a new type of lysosomotropic carrier.
Couvreur P, Tulkens P, Roland M, Trouet A, Speiser P.

J Pharm Pharmacol. 1979 May;31(5):331-2.
Polycyanoacrylate nanocapsules as potential lysosomotropic carriers: preparation, morphological and sorptive properties
Couvreur P, Kante B, Roland M, Guiot P, Bauduin P, Speiser P.

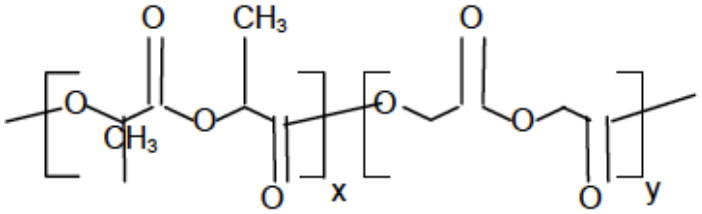
Poly-DL-lactide



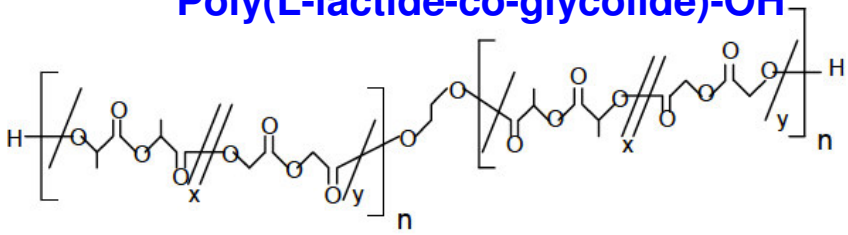
Poly(glycolide)



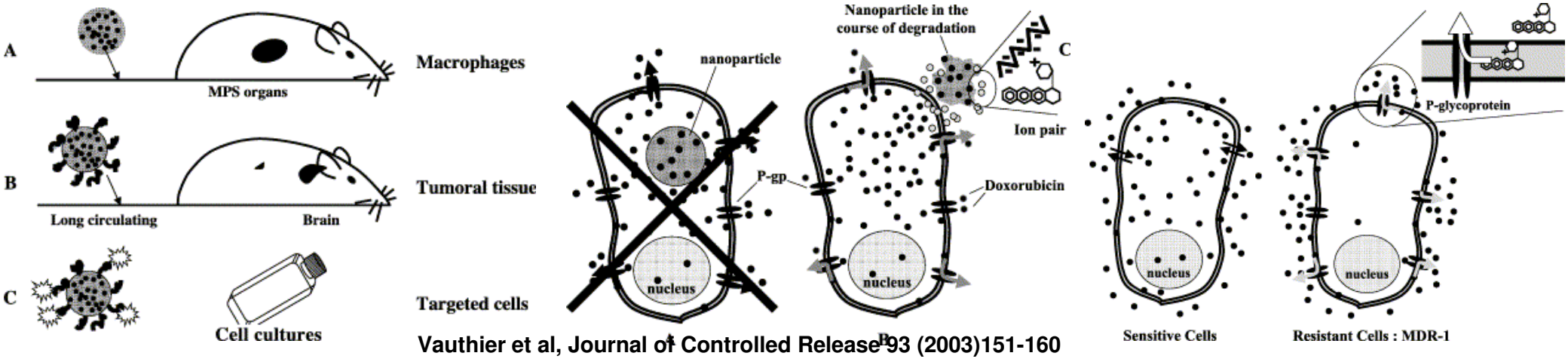
Poly(DL-lactide-co-glycolide)
Poly(L-lactide-co-glycolide)
Poly(glycolide-co-L-lactide)



Poly(DL-lactide-co-glycolide)-OH
Poly(L-lactide-co-glycolide)-OH



Polymeric nanoparticles: cancer



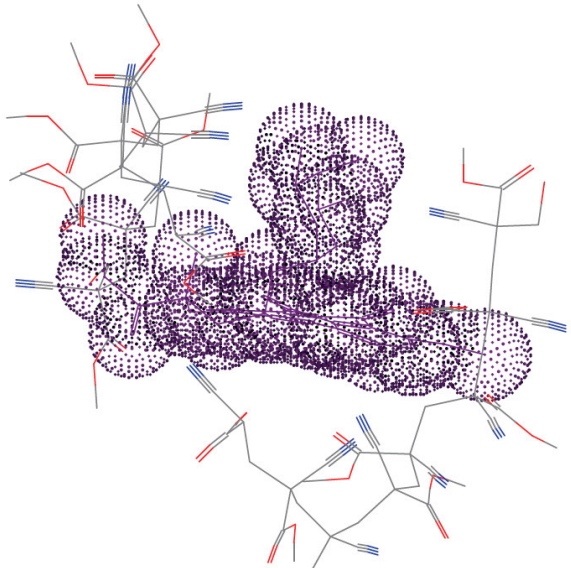
Vauthier et al, Journal of Controlled Release 93 (2003)151-160

Investigational New Drugs **10**: 191-199, 1992.

Phase I clinical trial and pharmacokinetic evaluation of doxorubicin carried by polyisohexylcyanoacrylate nanoparticles

Joseph Kattan[1], Jean-Pierre Droz[1], Patrick Couvreur[2], Jean-Pierre Marino[3], Arnaud Boutan-Laroze[1], Philippe Rougier[1], Philippe Brault[1], Henri Vranckx[4], Jean-Marc Grognet[5], Xavier Morge[5], Hélène Sancho-Garnier[6]

[1] *Department of Medicine, Institut Gustave-Roussy, Villejuif, France*; [2] *Laboratoire de Pharmacie Galenique et Biopharmacie, URA, CNRS, 1218, Université Paris XI, Chatenay-Malabry, France*; [3] *Centre de Diagnostic et Prévention Neuro-Vasculaire, Paris, France;* [4] *SOPAR S.A.B. - 1080, Brussels, Belgium*; [5] *Service de Pharmacologie et d'Immunologie, CEA, CE/Saclay, Gif-sur-Yvette, France*; [6] *Department of Statistics and Epidemiology, Institut Gustave-Roussy, Villejuif, France*



Poupaert and Couvreur,
Journal of Controlled Release 92 (2003) 19–26

Nanoparticles pipeline (overview)

Type of carrier and mean diameter (nm)	Drug entrapped or linked	Current stage of development	Type of cancer (for clinical trials)
Polymer–drug conjugates (6–15)	Doxorubicin, Paclitaxel, Camptothecin, Platinate, TNP-470	12 products under clinical trials (Phases I–III) and *in vivo*	Various tumours
Liposomes (both PEG and non-PEG coated) (85–100)	Lurtotecan, platinum compounds, Annamycin	Several products in clinical trials (Phases I–III) and *in vivo*	Solid tumours, renal cell carcinoma, mesothelioma, ovarian and acute lymphoblastic leukaemia
Polymeric nanoparticles (50–200)	Doxorubicin, Paclitaxel, platinum-based drugs, Docetaxel	Several products are in clinical trials (Phases I–III) and *in vivo*	Adenocarcinoma of the oesophagus, metastatic breast cancer and acute lymphoblastic leukemia
Polymersomes (~100)	Doxorubicin, Paclitaxel	*In vivo*	
Micelles (lipid based and polymeric) (5–100)	Doxorubicin	Clinical trials (Phase I)	Metastatic or recurrent solid tumours refractory to conventional chemotherapy
	Paclitaxel	Clinical trials (Phase I)	Pancreatic, bile duct, gastric and colonic cancers
	Platinum-based drugs (carboplatin/ cisplatin), Camptothecin, Tamoxifen, Epirubicin	*In vivo* and *in vitro*	
Nanoshells (Gold-silica) (~130)	No drug (for photothermal therapy)	*In vivo*	
Gold nanoparticles (10–40)	No drug (for photothermal ablation)	*In vivo*	
Nanocages (30–40)	No drug	Chemistry, structural analysis and *in vitro*	
Dendrimers (~ 5)	Methotrexate	*In vitro / in vivo*	
Immuno-PEG-liposomes (100)	Doxorubicin	Clinical trials (Phase I)	Metastatic stomach cancer
Immunoliposomes (100–150)	Doxorubicin, platinum-based drugs, Vinblastin, Vincristin, Topotecan, Paclitaxel	*In vivo*	
Immunotoxins, Immunopolymers, and fusion proteins (3–15)	Various drugs, toxins	Clinical trials (Phases I–III)	Various types of cancer

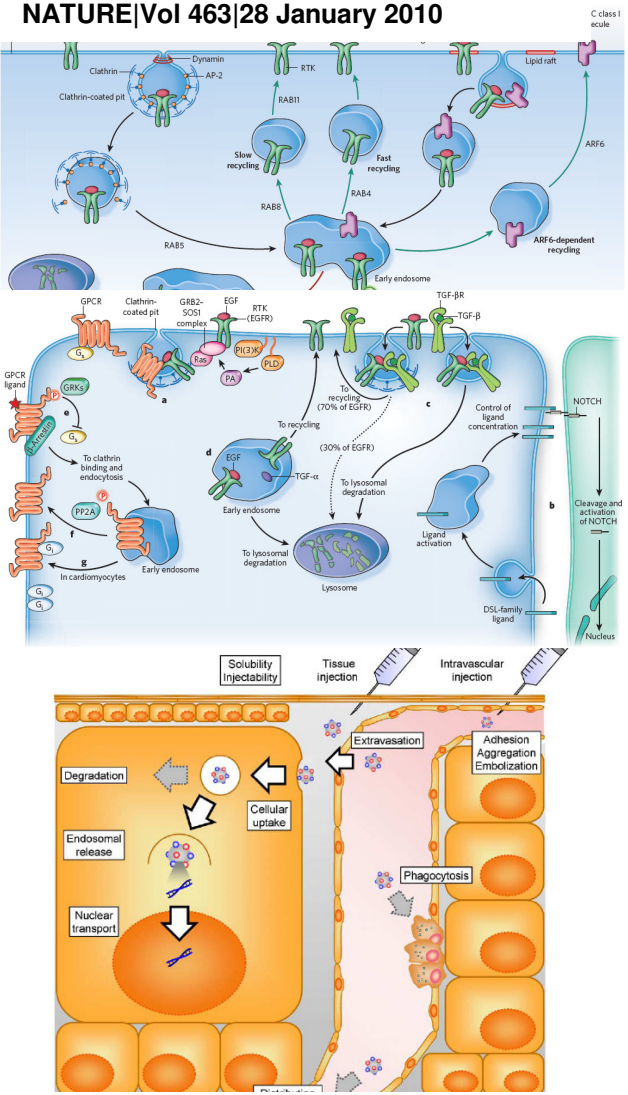
Nanocarriers as an emerging platform for cancer therapy,
D.Peer, J. M. Karp,S. Hong, O. C. Farokhzad,R. Margalit and Robert Langer, nature nanotechnology | VOL 2 | DECEMBER 2007 |

Key factors for design
(in respect of specific medical use)

- Materials Science and Formulation (Technology)
- Understanding underlying basic molecular mechanisms
- Integrating anatomo-physiological issues with pathology or disease state and its progression
- Changes in biological interactions
- Impact in toxicity and efficacy
- Relevance of animal models (In vitro ??! In vivo !!?)
- Differences both in Pharmacokinetics and Pharmacodynamics
- Translational models adapted to specific questions with “nano” (PK/PD versus specific organ toxicity and differential uptake of particles – translocation)
- Important issues in clinical development: How to move faster and safer? Comparability towards specific therapeutic indication?

Specific challenges and opportunities

Giorgio Scita & Pier Paolo Di Fiore,
NATURE|Vol 463|28 January 2010

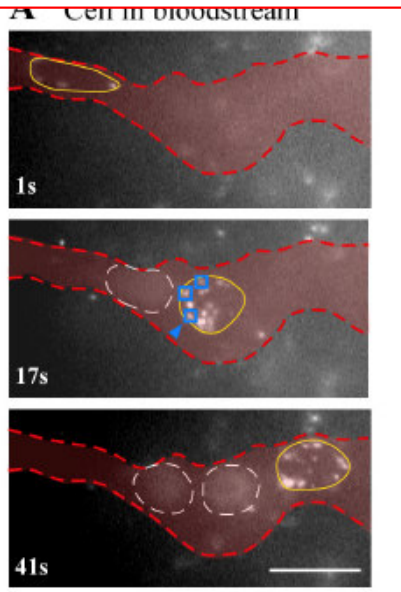


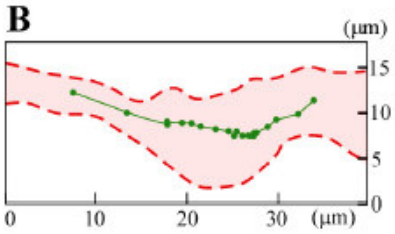
Nishikawa et al., Adv. Drug Deliv. Rev. 57(2005): 675-688

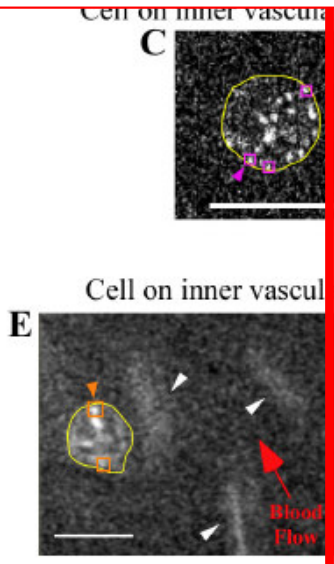
- **site-specific targeting**
  - Organ
  - Tissue
  - Cell
  - Intracellular
- **cytosolic delivery**
  - Endocytosis molecular mechanisms and how to take advantage for different strategies (siRNA, cytosolic receptor blockade, mithocondrial targeting)
  - Materials purposedly designed to overcome intracellular barriers for drug delivery
- **different routes of administration**
  - Parenteral
  - Oral
  - Ocular/Mucosal delivery, Dermal
- **new materials**

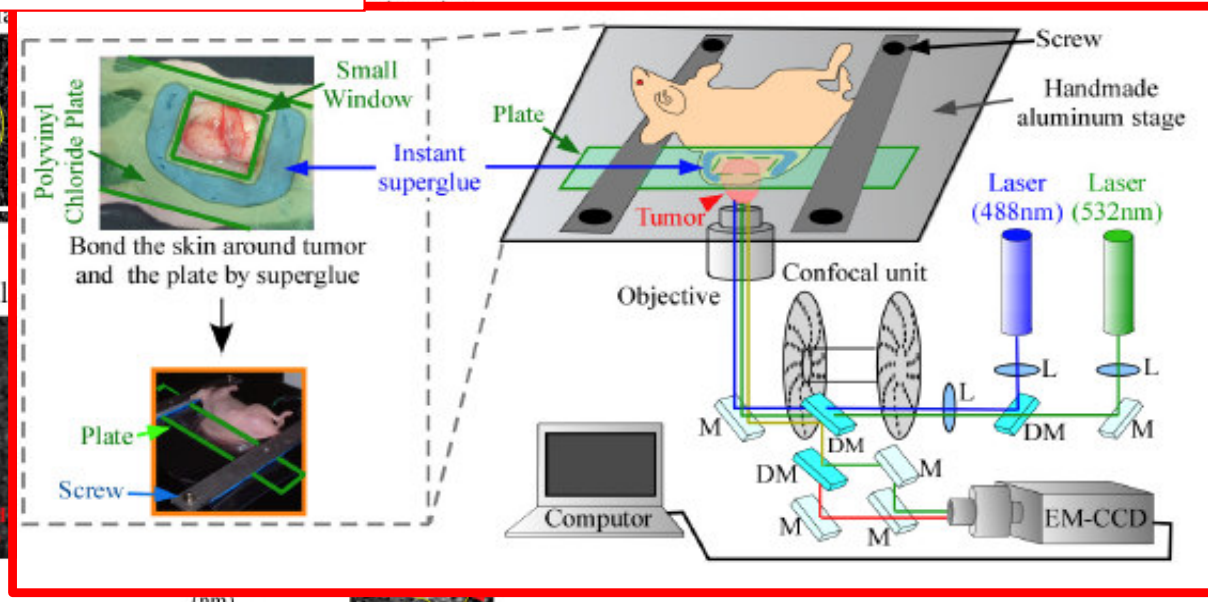
Emerging technologies

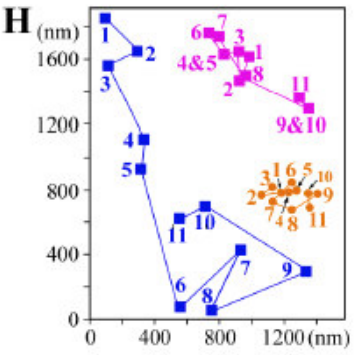
In vivo nano-imaging of membrane dynamics in metastatic tumor cells using quantum dots.
Gonda K, Watanabe TM, Ohuchi N, Higuchi H. (Tohoku University, Sendai, Japan) **J.Biol.Chem. Papers in Press.**
Published on November 16, 2009 as Manuscript http://, www.jbc.org/cgi/doi/10.1074/jbc.M109.075374

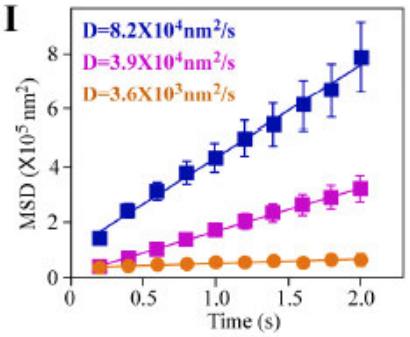


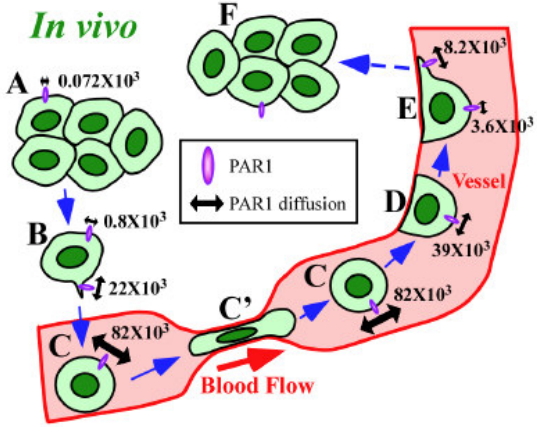












Specific challenges and opportunities

- **combination therapy**
  - The trend for reformulation of old APIs, with advantages of combined administration on the same delivery system (issues on quality/stability, PK/PD, clinical, IP, market access)

- **potential theranostic approaches**
  - Combined system that is able to localize to the target pathophysiology and deliver an appropriate therapeutic agent (both diagnostic and therapeutic functions)

- **“follow-on” products**
  - A number of unresolved problems will arise if preventive action is not taken on matters related to old products, previously not classified as nanoparticles that are in fact colloidal nanoparticulate systems

Iron oxide similars / Iron nanoparticles

- **A number medicinal products contaning iron oxide nanoparticles have been approved as "follow on" products (controversial data published in the literature)**

Roth et al, Translational Research 2008;151:36-44 (BfArm)

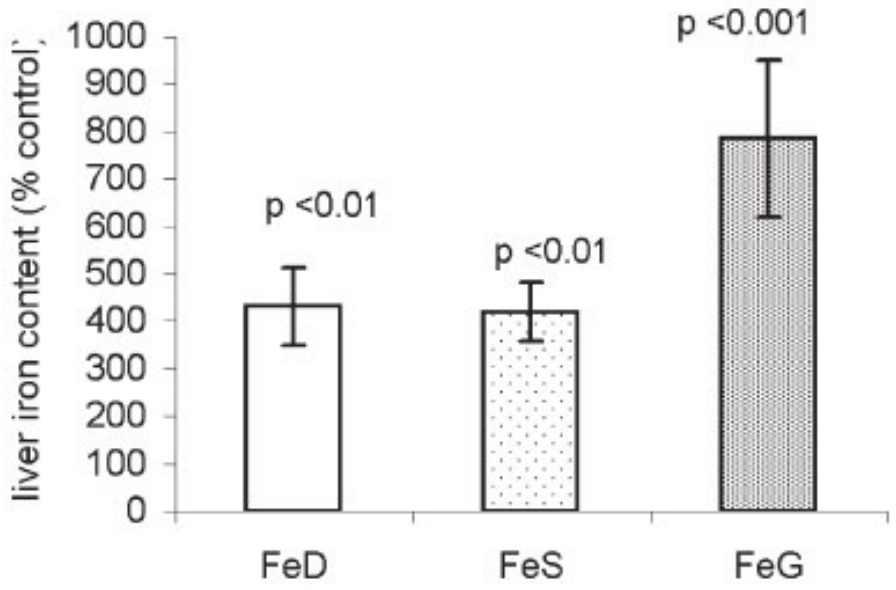


Fig 2. Mean liver iron content (in % of control ± SEM) after administration of FeD, FeS, and FeG that contains 8-mg Fe^{3+} to fertilized turkey eggs. Egg white injection, incubation time was 22 days. Statistical significance in comparison with control is shown.

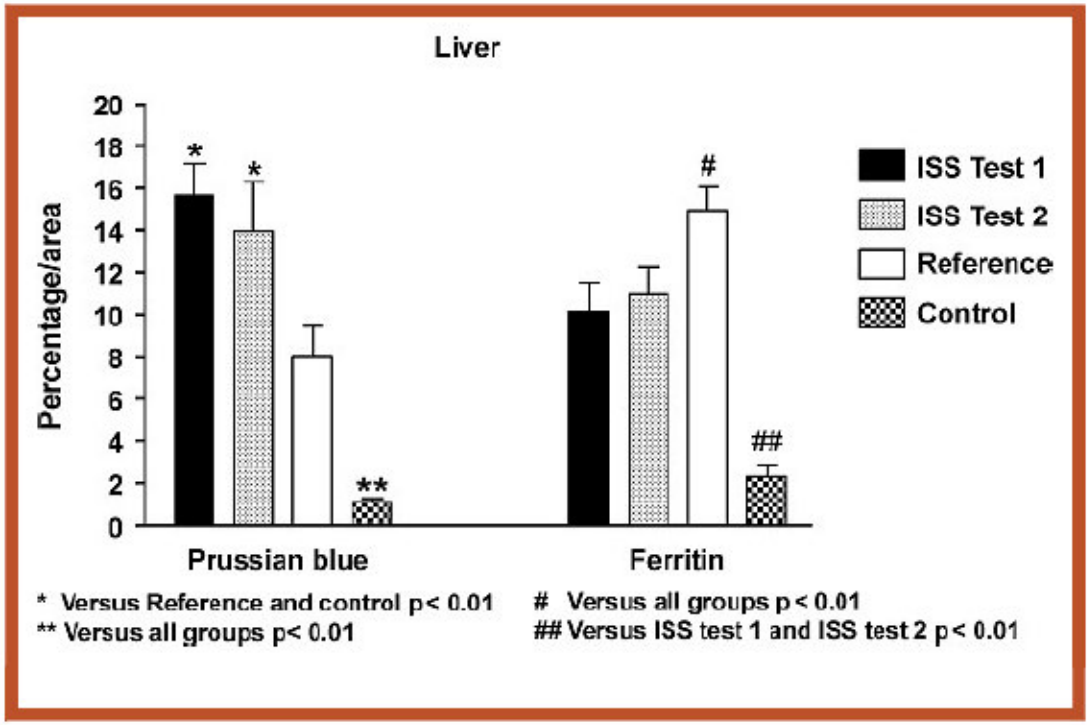


Fig. 6: Bar charts and micrographs showing Prussian blue staining for iron deposits and ferritin immunostaining for stored iron in liver samples taken from the ISS test 1, ISS test 2, reference and control groups on day 28.

Toblli et al, Arzneimittelforschung 2009;59(4):176–190

Issues

- **Materials Science**
  - Challenges arising from new materials (inorganic nanoparticles, non-biodegradable/ non-biocompatible materials, quantum dots, cationic particles and dendrimeric structures, carbon nanotubes)
- **Formulation / Technologies**
  - Adapting existing technologies to new opportunities (e.g. Quality by Design, Process Analytical Technologies)
- **Translational Research**
  - Adequacy of non-clinical methodology before first in man use (relevance of, appropriate toxicityfficcacy biomarkers and barriers related to disease phase and different routes of administration)
- **Clinical development**
  - Comparability: non-inferiority versus superiority (risk-benefit management)
- **Market Access**
  - Comparative pharmacoeconomic assessment

Risk management

(personal view presented previously during OECD Working Party in Nanotechnology, Vienna September 2009)

- ***What are the criteria used to decide that risk management actions are required?***
  - ***In the medicinal products sector well defined and implemented, not in the medical devices or other borderline areas…***
- ***How is scientific evidence and uncertainty reflected in subsequent risk management actions?***
  - ***In the medicinal products area integrated in the product life cycle permanent assessment***
- ***How are decisions taken? - and how transparent and predictable are they?***
  - ***Under established regulation framework for medicinal products, with well defined competences and enforcement modalities***
- ***To what extent is risk management science-based?***
  - ***Science-driven, based on data on medicinal products compiled with appropriate rules established under globally harmonized (USA, EU, Japan – ICH) guidelines; need care with situation regarding new engineered materials and combination products***