Nanoparticles for Drug Targeting: Current Status and Future

Gert Storm

Department of Pharmaceutics
Utrecht Institute for Pharmaceutical Sciences
Utrecht University

Department of Targeted Therapeutics
MIRA Institute for Biomedical Technology&Technical Medicine, University of Twente

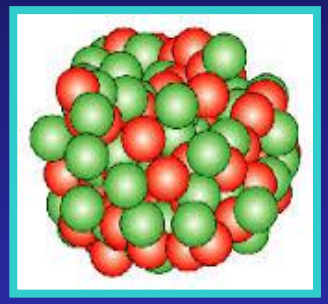
Universiteit Utrecht

UNIVERSITEIT TWENTE.

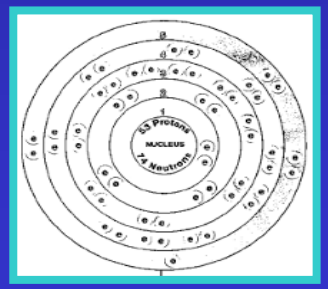
Mother Nature

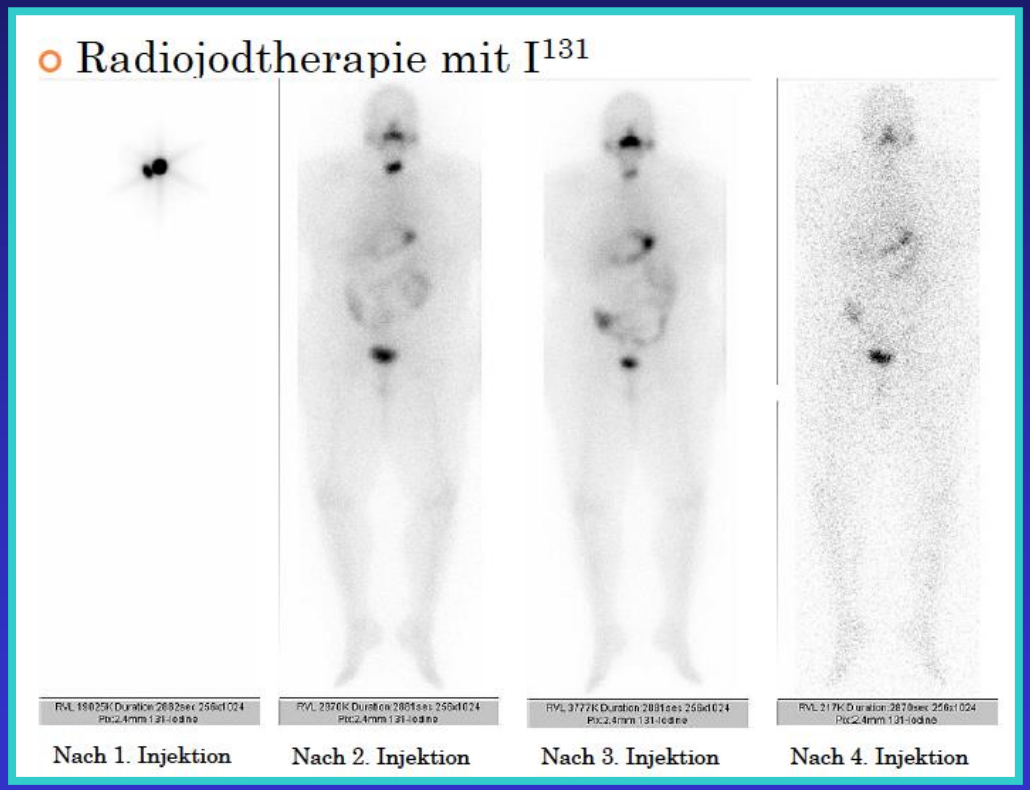
Iodide: almost 100% in the thyroids

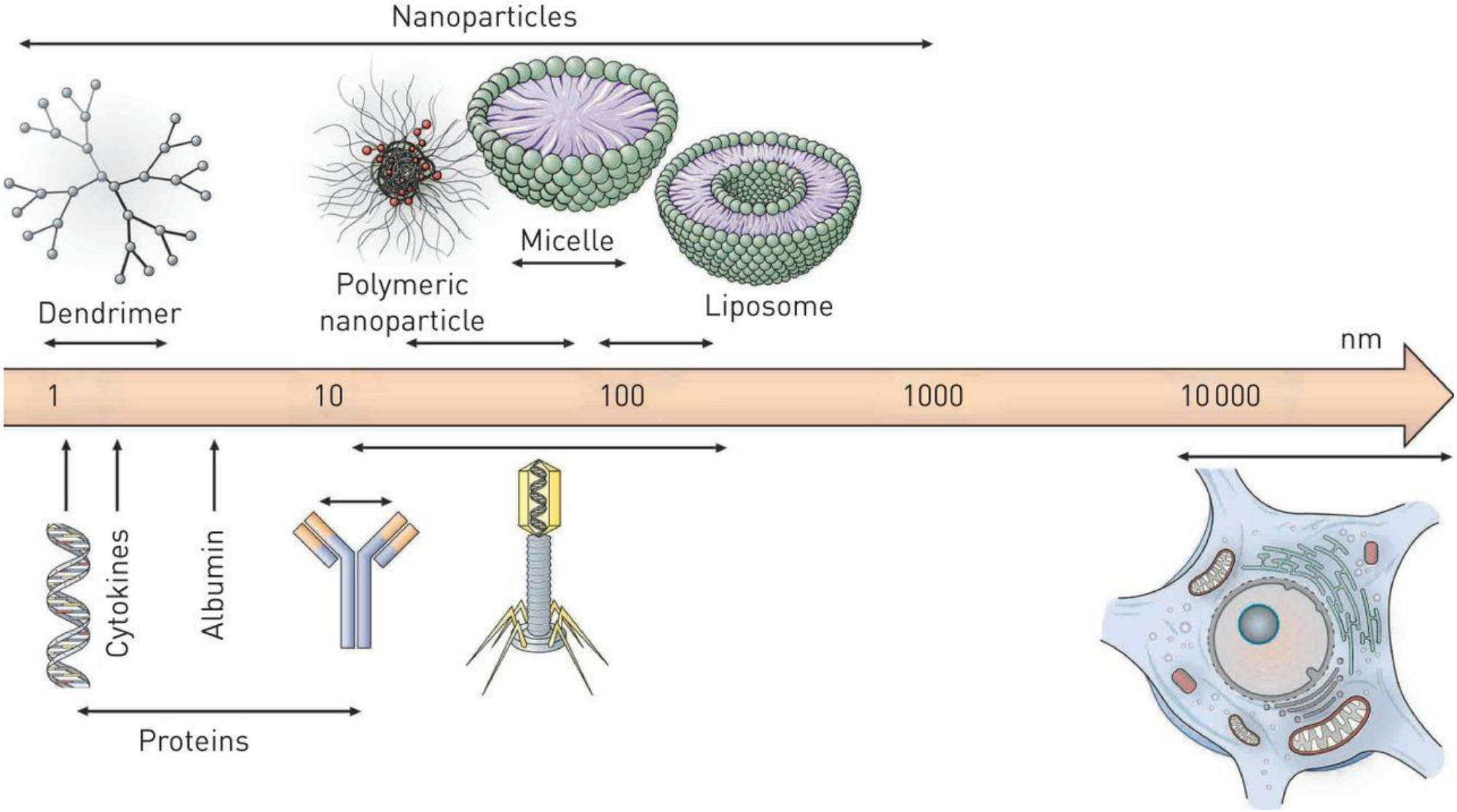
=> ^{131} iodine-based diagnosis and therapy of thyroid cancer



^{131}I = 0.1 nm






Nanoparticles
Dendrimer
Polymeric nanoparticle
Micelle
Liposome
nm
1
10
100
1000
10 000
Cytokines
Albumin
Proteins

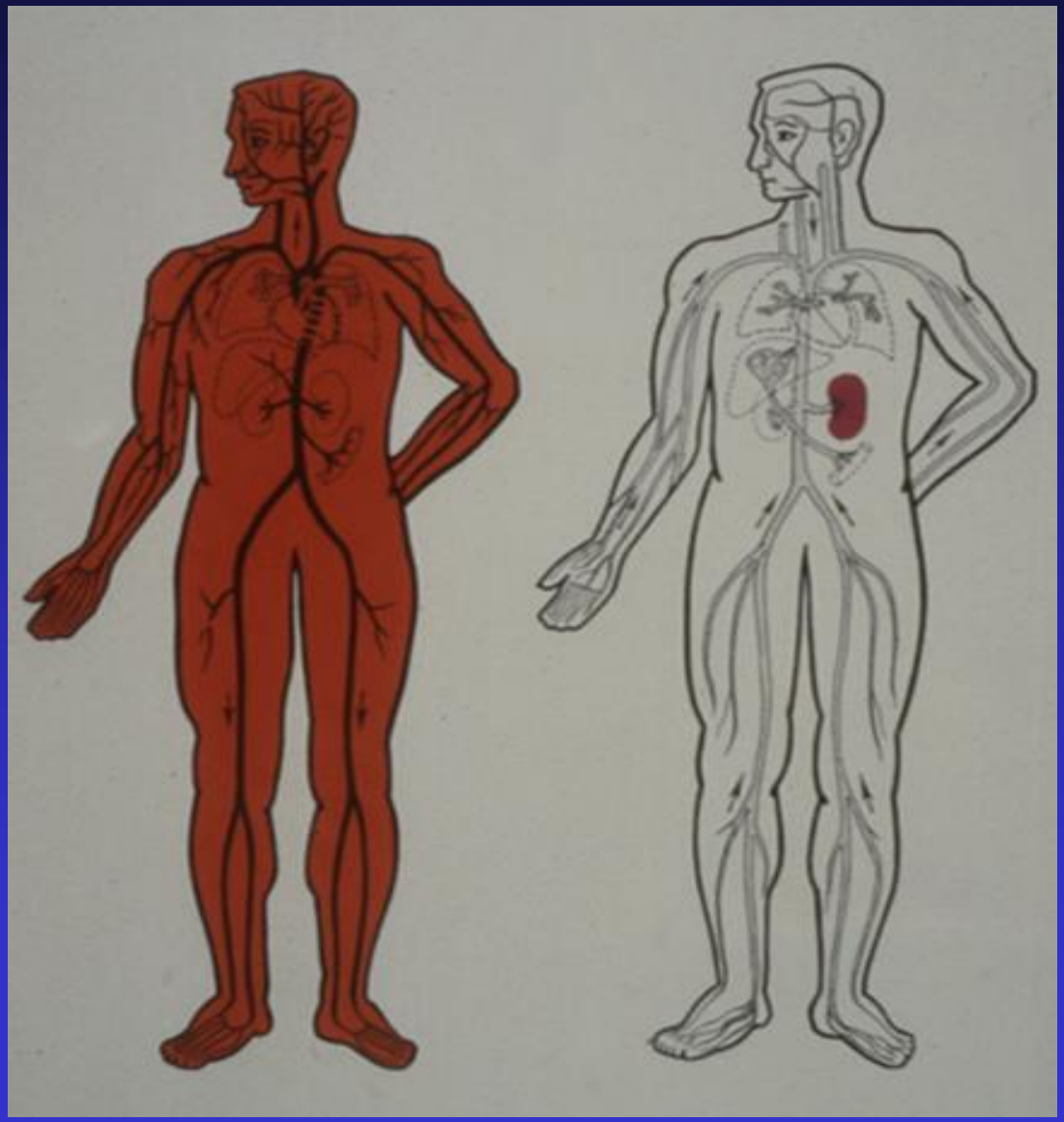

NOT A GANGSTER PICTURE BUT
. . . a war on the deadliest
public enemy of all!
EDWARD G.
ROBINSON
DR. EHRLICH'S MAGIC BULLET
RUTH GORDON · OTTO KRUGER · DONALD CRISP
Directed by WILLIAM DIETERLE · A WARNER BROS.-First National Picture
Presented by
WARNER BROS.

There's plenty of room at the bottom.

— Richard P. Feynman —

AZ QUOTES

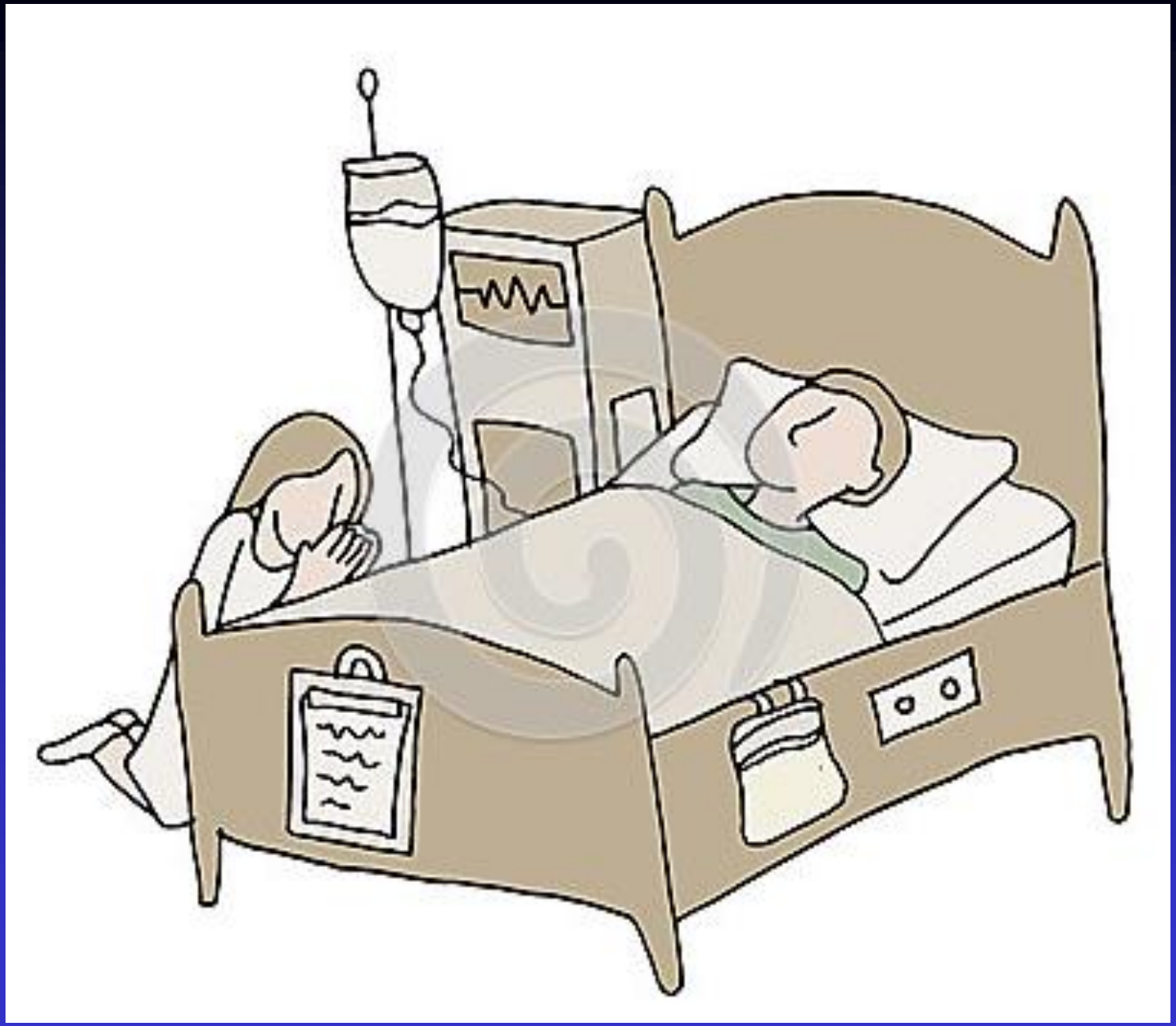
Targeted Nanomedicines



AIM: Increased Therapeutic Index

Efficacy / Toxicity

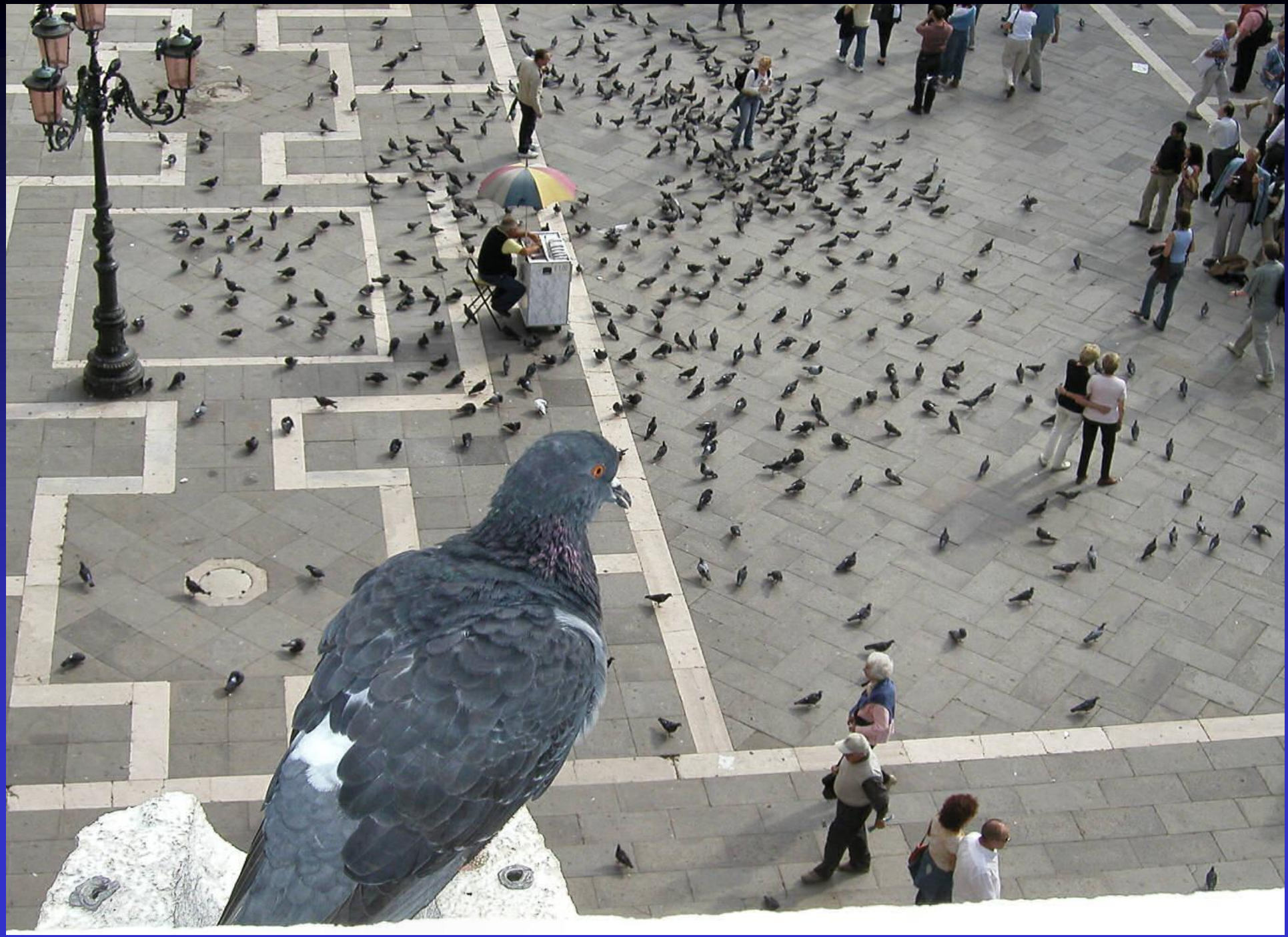
Targeted nanomedicines can favorably change the efficacy/safety balance



Life-threatening and society-burdening diseases:

needle often required

often drugs with small therapeutic index



Drug Targeting Routes

- Direct administration into diseased site (only possible in limited cases)

- Systemic administration (mostly parenteral administration)

70-90s: Major limitations of IV nanoparticulate drug targeting

- Short circulation time due to efficient MPS uptake
- Drug release in the bloodstream
- Limited capacity to extravasate

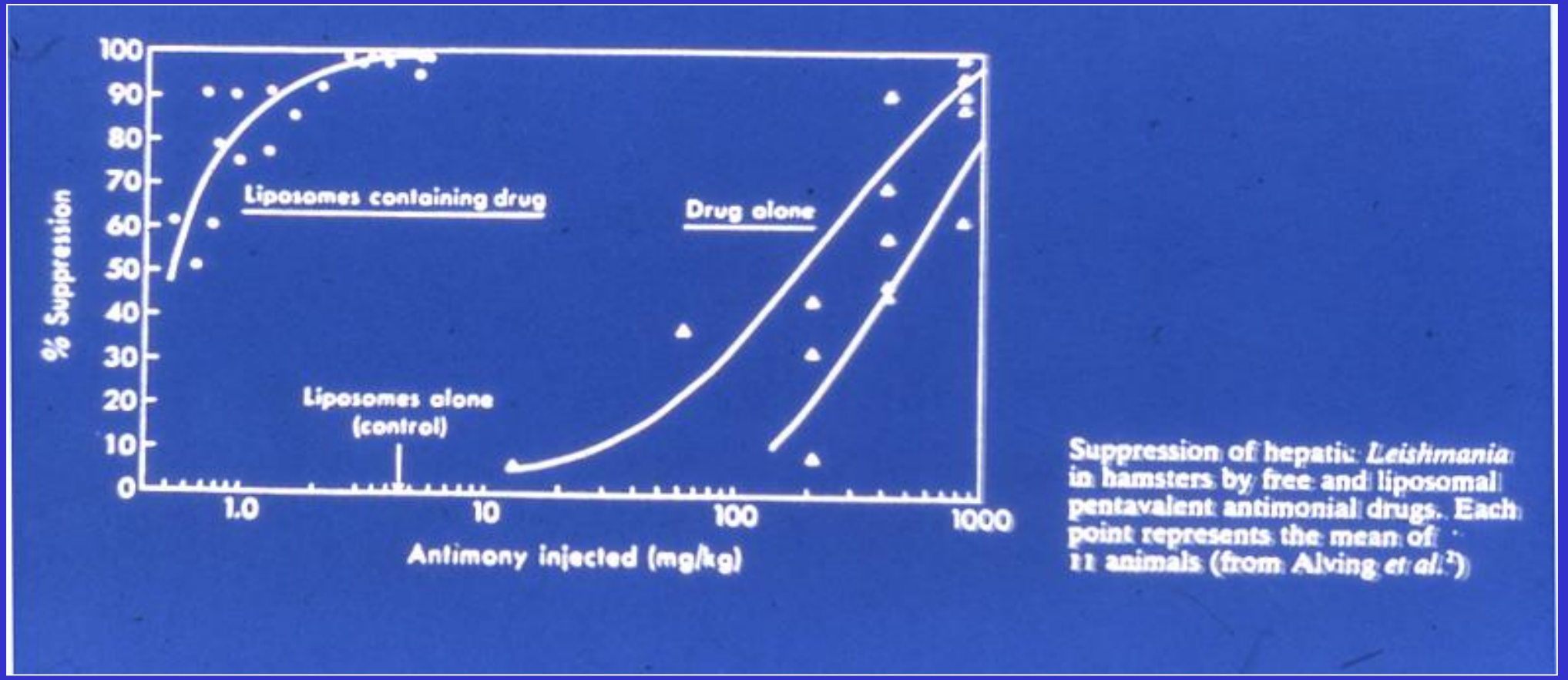
Nanoparticles are often rapidly removed from the circulation by phagocytic MPS cells (mainly those in liver and spleen).

Liver and spleen uptake

The macrophages in liver and spleen are mainly responsible for rapid clearance from the circulation

These macrophages are also the cell type of replication for many intracellular infectious organisms

(*Salmonella spp., Brucella spp., Mycobacterium spp., Leishmania spp.)*

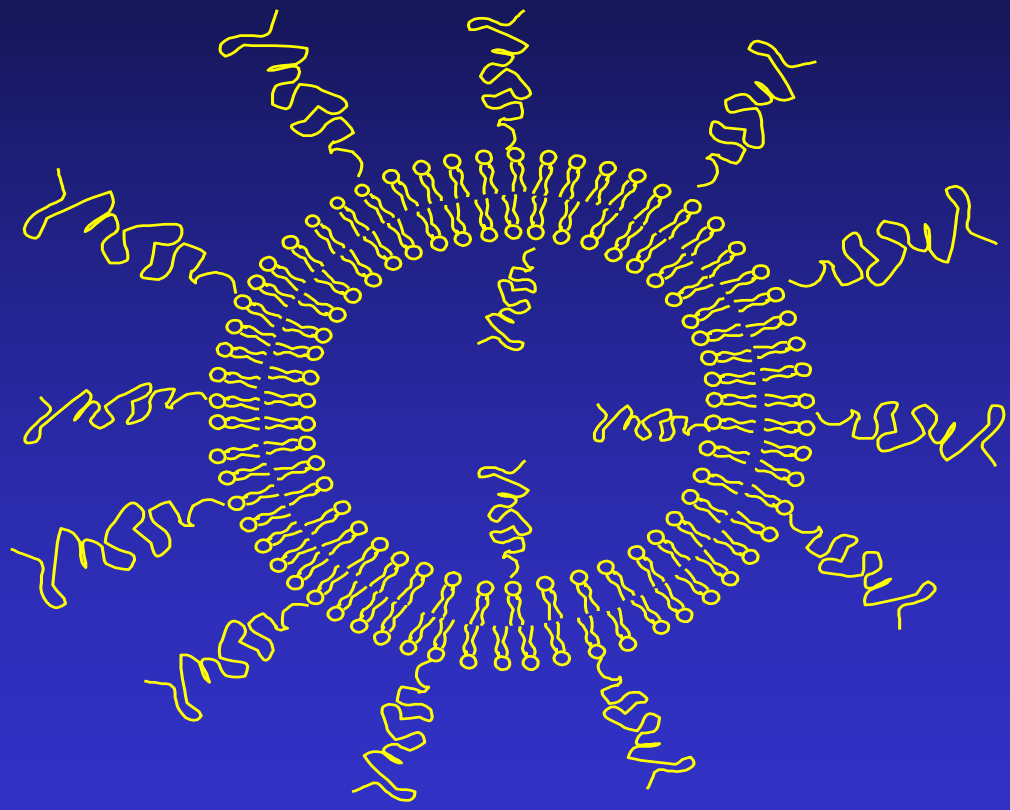


Suppression of hepatic *Leishmania* in hamsters by free and liposomal pentavalent antimonial drugs. Each point represents the mean of 11 animals (from Alving *et al.*[2])

Major limitations of IV nanoparticulate drug targeting

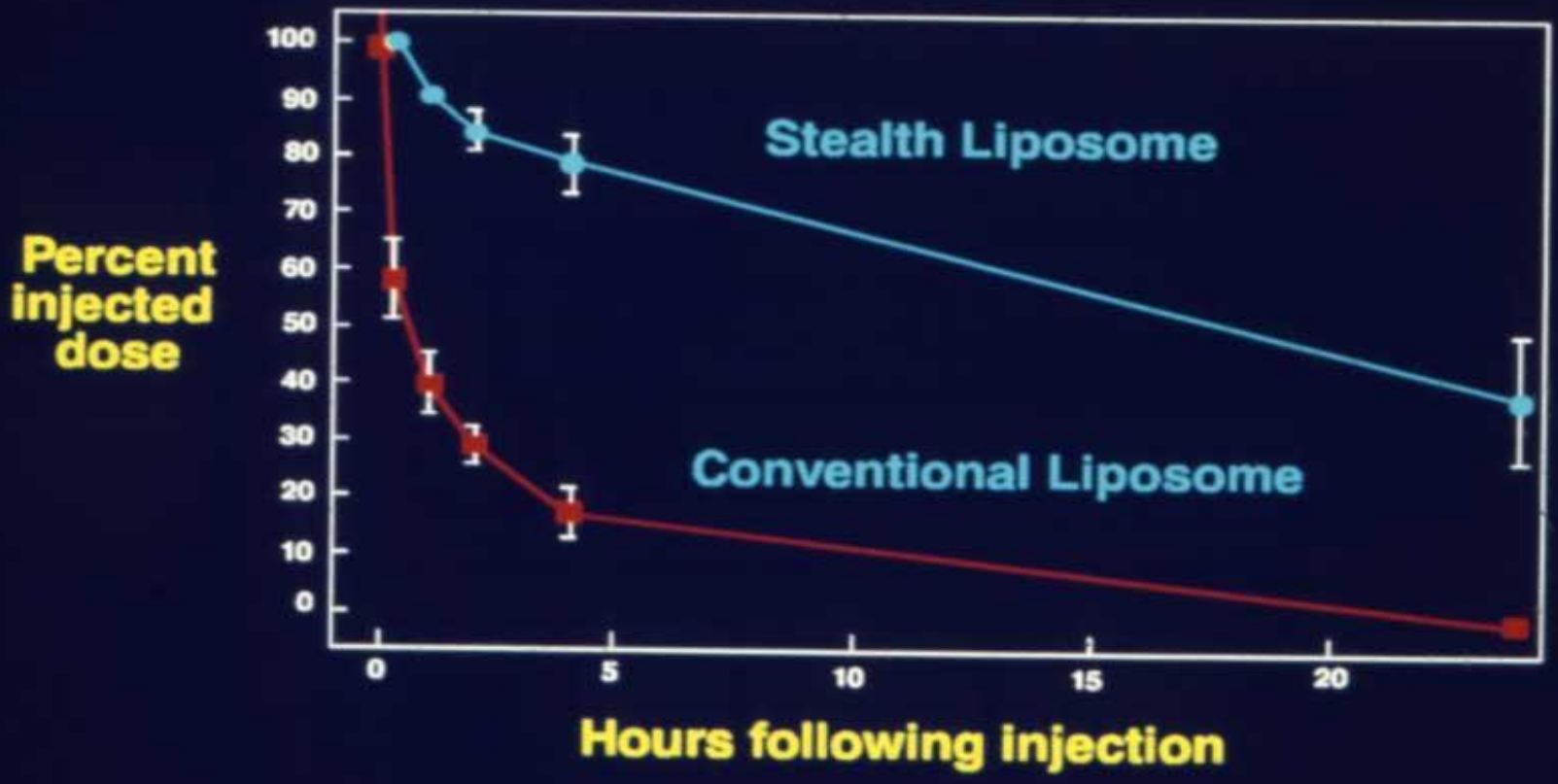
- Short circulation time due to efficient MPS uptake
- Limited capacity to extravasate

PEG coating prolongs liposome circulation time



Coating with poly(ethylene) glycol (PEG) decelerates liposome uptake by MPS

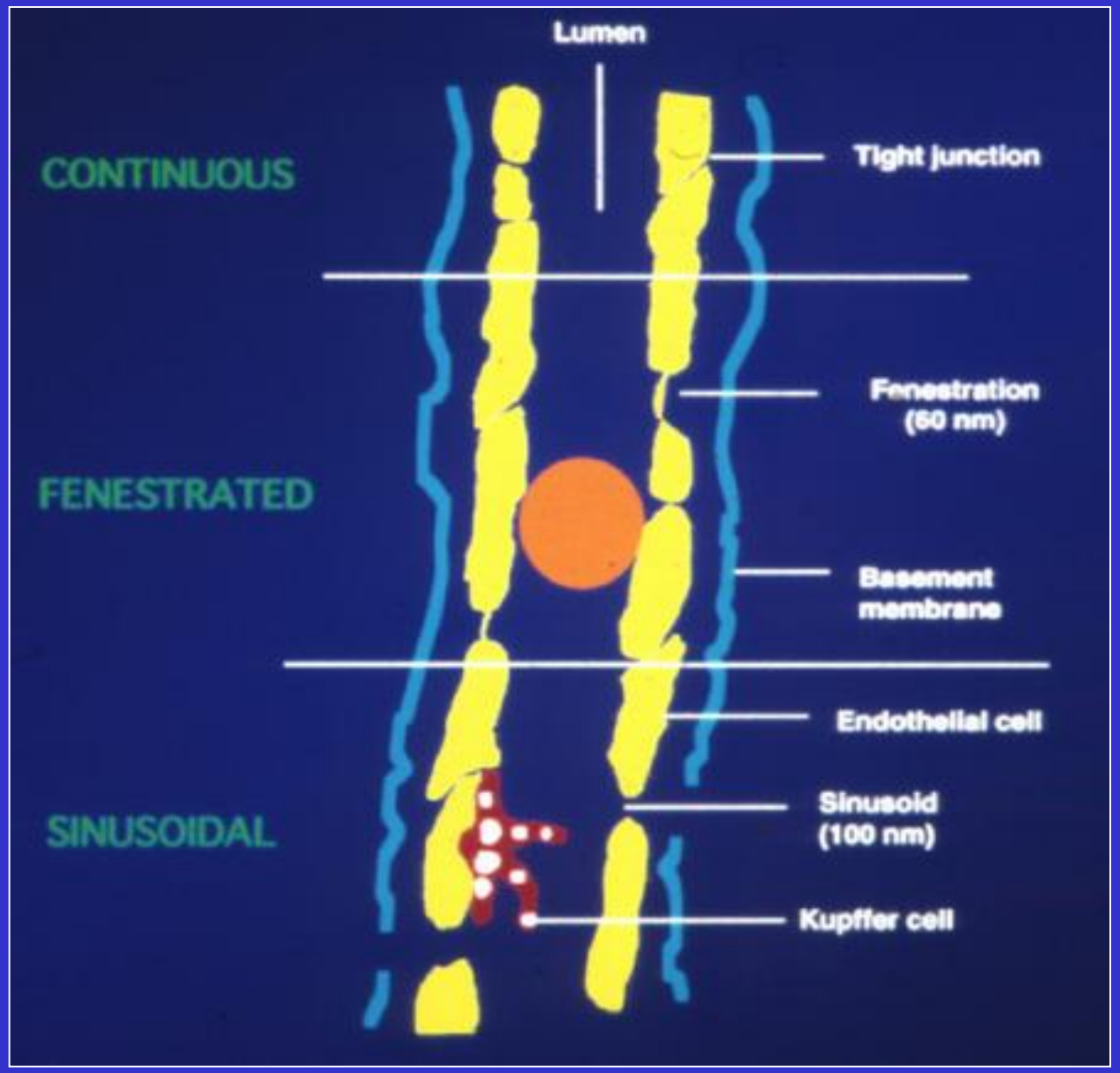
Plasma Clearance of Stealth® and Conventional Liposomes



Major limitations of IV nanoparticulate drug targeting

- Short circulation time due to efficient MPS uptake
- Limited capacity to extravasate

The Endothelial Barrier



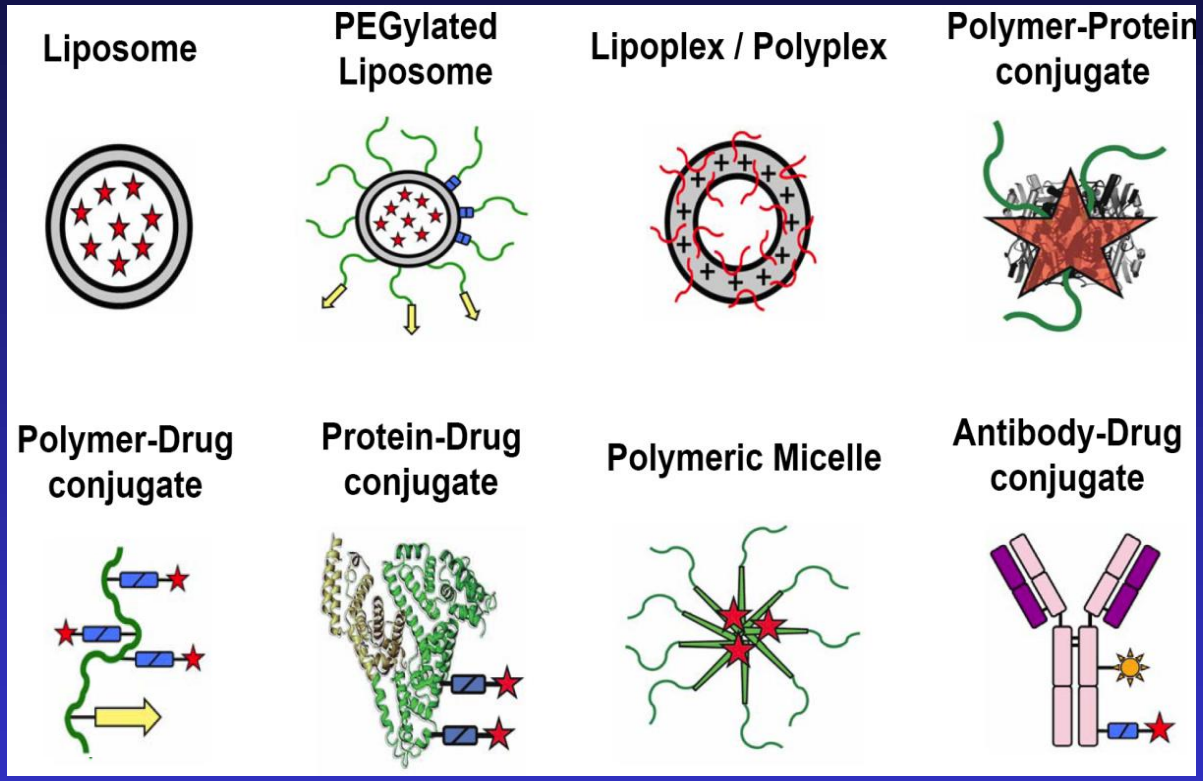
Endothelium in disease

In many disease processes the endothelium becomes permeable (inflammation, infection, malignancy)

allowing EXTRAVASATION

Extravasation through ‘leaky’ vasculature (EPR effect)

Targeted Nanomedicines In Clinical Application

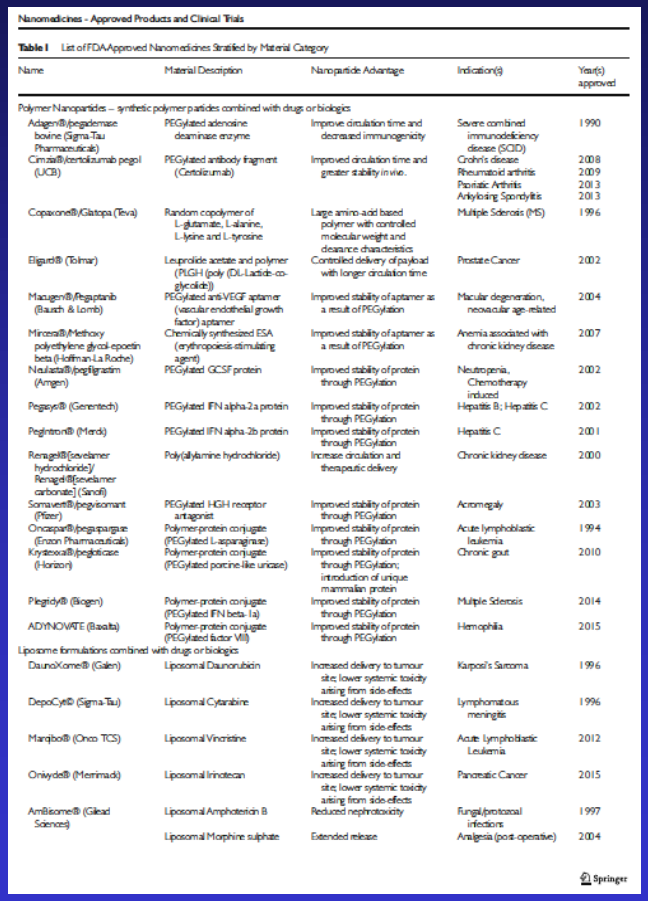


Universiteit Utrecht

UIPS Utrecht Institute for Pharmaceutical Sciences

nanomedicines on the market (about 50)

nanocrystals (15/0) + polymers (15/2) + liposomes (10/4)
+ proteins (2/2) + micelles (1/0) + inorganic NP (8/1)



Nanomedicines - Approved Products and Clinical Trials

Table I List of FDA-Approved Nanomedicines Stratified by Material Category

Name	Material Description	Nanoparticle Advantage	Indication(s)	Year(s) approved
Polymer Nanoparticles – synthetic polymer particles combined with drugs or biologics				
Adagen®/pegademase bovine (Sigma-Tau Pharmaceuticals)	PEGylated adenosine deaminase enzyme	Improve circulation time and decreased immunogenicity	Severe combined immunodeficiency disease (SCID)	1990
Cimzia®/certolizumab pegol (UCB)	PEGylated antibody fragment (Certolizumab)	Improved circulation time and greater stability in vivo.	Crohn's disease Rheumatoid arthritis Psoriatic Arthritis Ankylosing Spondylitis	2008 2009 2013 2013
Copaxone®/Glatopa (Teva)	Random copolymer of L-glutamate, L-alanine, L-lysine and L-tyrosine	Large amino-acid based polymer with controlled molecular weight and clearance characteristics	Multiple Sclerosis (MS)	1996
Eligard® (Tolmar)	Leuprolide acetate and polymer (PLGH (poly (DL-Lactide-co-glycolide))	Controlled delivery of payload with longer circulation time	Prostate Cancer	2002
Macugen®/Pegaptanib (Bausch & Lomb)	PEGylated anti-VEGF aptamer (vascular endothelial growth factor) aptamer	Improved stability of aptamer as a result of PEGylation	Macular degeneration, neovascular age-related	2004
Mircera®/Methoxy polyethylene glycol-epoetin beta (Hoffman-La Roche)	Chemically synthesized ESA (erythropoiesis-stimulating agent)	Improved stability of aptamer as a result of PEGylation	Anemia associated with chronic kidney disease	2007
Neulasta®/pegfilgrastim (Amgen)	PEGylated GCSF protein	Improved stability of protein through PEGylation	Neutropenia, Chemotherapy induced	2002
Pegasys® (Genentech)	PEGylated IFN alpha-2a protein	Improved stability of protein through PEGylation	Hepatitis B; Hepatitis C	2002
Pegintron® (Merck)	PEGylated IFN alpha-2b protein	Improved stability of protein through PEGylation	Hepatitis C	2001
Renagel®(sevelamer hydrochloride)/ Renagel®(Sevelamer carbonate) (Sanofi)	Poly(allylamine hydrochloride)	Increase circulation and therapeutic delivery	Chronic kidney disease	2000
Somavert®/pegvisomant (Pfizer)	PEGylated HGH receptor antagonist	Improved stability of protein through PEGylation	Acromegaly	2003
Oncaspar®/pegaspargase (Enzon Pharmaceuticals)	Polymer-protein conjugate (PEGylated L-asparaginase)	Improved stability of protein through PEGylation	Acute lymphoblastic leukemia	1994
Krystexxa®/pegloticase (Horizon)	Polymer-protein conjugate (PEGylated porcine-like uricase)	Improved stability of protein through PEGylation; introduction of unique mammalian protein	Chronic gout	2010
Plegridy® (Biogen)	Polymer-protein conjugate (PEGylated IFN beta- 1a)	Improved stability of protein through PEGylation	Multiple Sclerosis	2014
ADYNOVATE (Baxalta)	Polymer-protein conjugate (PEGylated factor VIII)	Improved stability of protein through PEGylation	Hemophilia	2015
Liposome formulations combined with drugs or biologics				
DaunoXome® (Galen)	Liposomal Daunorubicin	Increased delivery to tumour site; lower systemic toxicity arising from side-effects	Kaposi's Sarcoma	1996
DepoCyt® (Sigma-Tau)	Liposomal Cytarabine	Increased delivery to tumour site; lower systemic toxicity arising from side-effects	Lymphomatous meningitis	1996
Marqibo® (Onco TCS)	Liposomal Vincristine	Increased delivery to tumour site; lower systemic toxicity arising from side-effects	Acute Lymphoblastic Leukemia	2012
Onivyde® (Merrimack)	Liposomal Irinotecan	Increased delivery to tumour site; lower systemic toxicity arising from side-effects	Pancreatic Cancer	2015
AmBisome® (Gilead Sciences)	Liposomal Amphotericin B	Reduced nephrotoxicity	Fungal/protozoal infections	1997
	Liposomal Morphine sulphate	Extended release	Analgesia (post-operative)	2004

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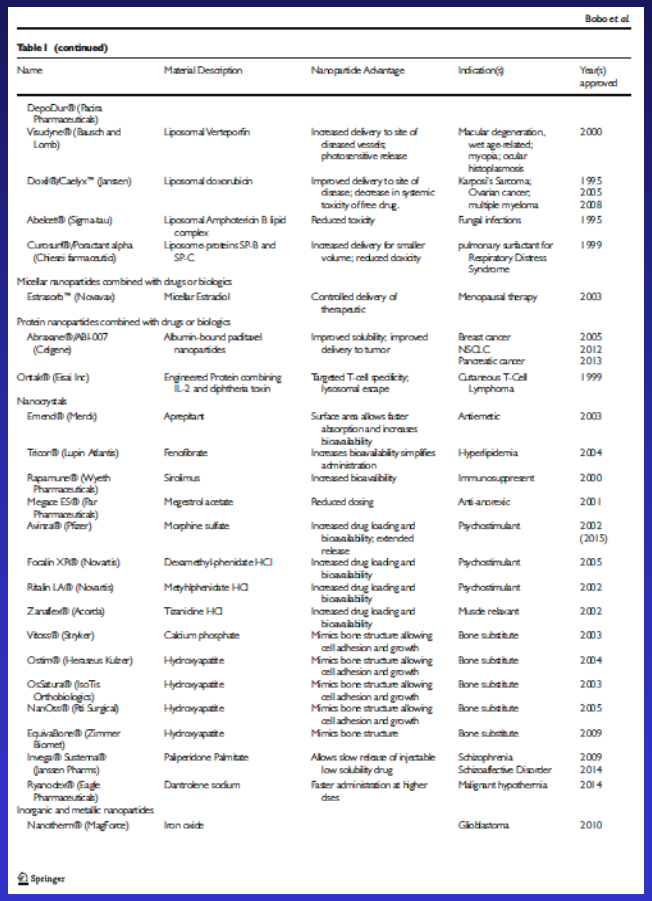
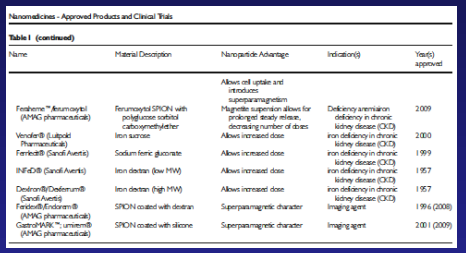


Bobo et al.

Table I (continued)

Name	Material Description	Nanoparticle Advantage	Indication(s)	Year(s) approved
DepoDur® (Pacira Pharmaceuticals)				
Visudyne® (Bausch and Lomb)	Liposomal Verteporfin	Increased delivery to site of diseased vessels; photosensitive release	Macular degeneration, wet age-related; myopia; ocular histoplasmosis	2000
Doxil®/Caelyx™ (Janssen)	Liposomal doxorubicin	Improved delivery to site of disease; decrease in systemic toxicity of free drug.	Kaposi's Sarcoma; Ovarian cancer; multiple myeloma	1995 2005 2008
Abelcet® (Sigma-tau)	Liposomal Amphotericin B lipid complex	Reduced toxicity	Fungal infections	1995
Curosurf®/Poractant alpha (Chiesi farmaceutici)	Liposome-proteins SP-B and SP-C	Increased delivery for smaller volume; reduced doxicity	pulmonary surfactant for Respiratory Distress Syndrome	1999
Micellar nanoparticles combined with drugs or biologics				
Estrasorb™ (Novavax)	Micellar Estradiol	Controlled delivery of therapeutic	Menopausal therapy	2003
Protein nanoparticles combined with drugs or biologics				
Abraxane®/ABI-007 (Celgene)	Albumin-bound paclitaxel nanoparticles	Improved solubility; improved delivery to tumor	Breast cancer NSCLC Pancreatic cancer	2005 2012 2013
Ontak® (Eisai Inc)	Engineered Protein combining IL-2 and diphtheria toxin	Targeted T-cell specificity; lysosomal escape	Cutaneous T-Cell Lymphoma	1999
Nanocrystals				
Emend® (Merck)	Aprepitant	Surface area allows faster absorption and increases bioavailability	Antiemetic	2003
Tricor® (Lupin Atlantis)	Fenofibrate	Increases bioavailability simplifies administration	Hyperlipidemia	2004
Rapamune® (Wyeth Pharmaceuticals)	Sirolimus	Increased bioavailability	Immunosuppresent	2000
Megace ES® (Par Pharmaceuticals)	Megestrol acetate	Reduced dosing	Anti-anorexic	2001
Avinza® (Pfizer)	Morphine sulfate	Increased drug loading and bioavailability; extended release	Psychostimulant	2002 (2015)
Focalin XR® (Novartis)	Dexamethyl-phenidate HCl	Increased drug loading and bioavailability	Psychostimulant	2005
Ritalin LA® (Novartis)	Methylphenidate HCl	Increased drug loading and bioavailability	Psychostimulant	2002
Zanaflex® (Acorda)	Tizanidine HCl	Increased drug loading and bioavailability	Muscle relaxant	2002
Vitoss® (Stryker)	Calcium phosphate	Mimics bone structure allowing cell adhesion and growth	Bone substitute	2003
Ostim® (Heraeus Kulzer)	Hydroxyapatite	Mimics bone structure allowing cell adhesion and growth	Bone substitute	2004
OsSatura® (IsoTis Orthobiologics)	Hydroxyapatite	Mimics bone structure allowing cell adhesion and growth	Bone substitute	2003
NanOss® (Rti Surgical)	Hydroxyapatite	Mimics bone structure allowing cell adhesion and growth	Bone substitute	2005
EquivaBone® (Zimmer Biomet)	Hydroxyapatite	Mimics bone structure	Bone substitute	2009
Invega® Sustenna® (Janssen Pharms)	Paliperidone Palmitate	Allows slow release of injectable low solubility drug	Schizophrenia Schizoaffective Disorder	2009 2014
Ryanodex® (Eagle Pharmaceuticals)	Dantrolene sodium	Faster administration at higher dses	Malignant hypothermia	2014
Inorganic and metallic nanoparticles				
Nanotherm® (MagForce)	Iron oxide		Glioblastoma	2010

Springer



Nanomedicines - Approved Products and Clinical Trials

Table I (continued)

Name	Material Description	Nanoparticle Advantage	Indication(s)	Year(s) approved
		Allows cell uptake and introduces superparamagnetism		
Feraheme™/Ferumoxytol (AMAG pharmaceutical)	Ferumoxytol SPION with polyglucose sorbitol carboxymethylether	Magnetite suspension allows for prolonged steady release, decreasing number of doses	Deficiency anemiairon deficiency in chronic kidney disease (CKD)	2009
Venofer® (Luitpold Pharmaceuticals)	Iron sucrose	Allows increased dose	iron deficiency in chronic kidney disease (CKD)	2000
Ferrlecit® (Sanofi Aventis)	Sodium ferric gluconate	Allows increased dose	iron deficiency in chronic kidney disease (CKD)	1999
INFeD® (Sanofi Aventis)	Iron dextran (low MW)	Allows increased dose	iron deficiency in chronic kidney disease (CKD)	1957
Dexiron®/Dexferrum® (Sanofi Aventis)	Iron dextran (high MW)	Allows increased dose	iron deficiency in chronic kidney disease (CKD)	1957
Feridex®/Endorem® (AMAG pharmaceutical)	SPION coated with dextran	Superparamagnetic character	Imaging agent	1996 (2008)
GastroMARK™/umirem® (AMAG pharmaceutical)	SPION coated with silicone	Superparamagnetic character	Imaging agent	2001 (2009)

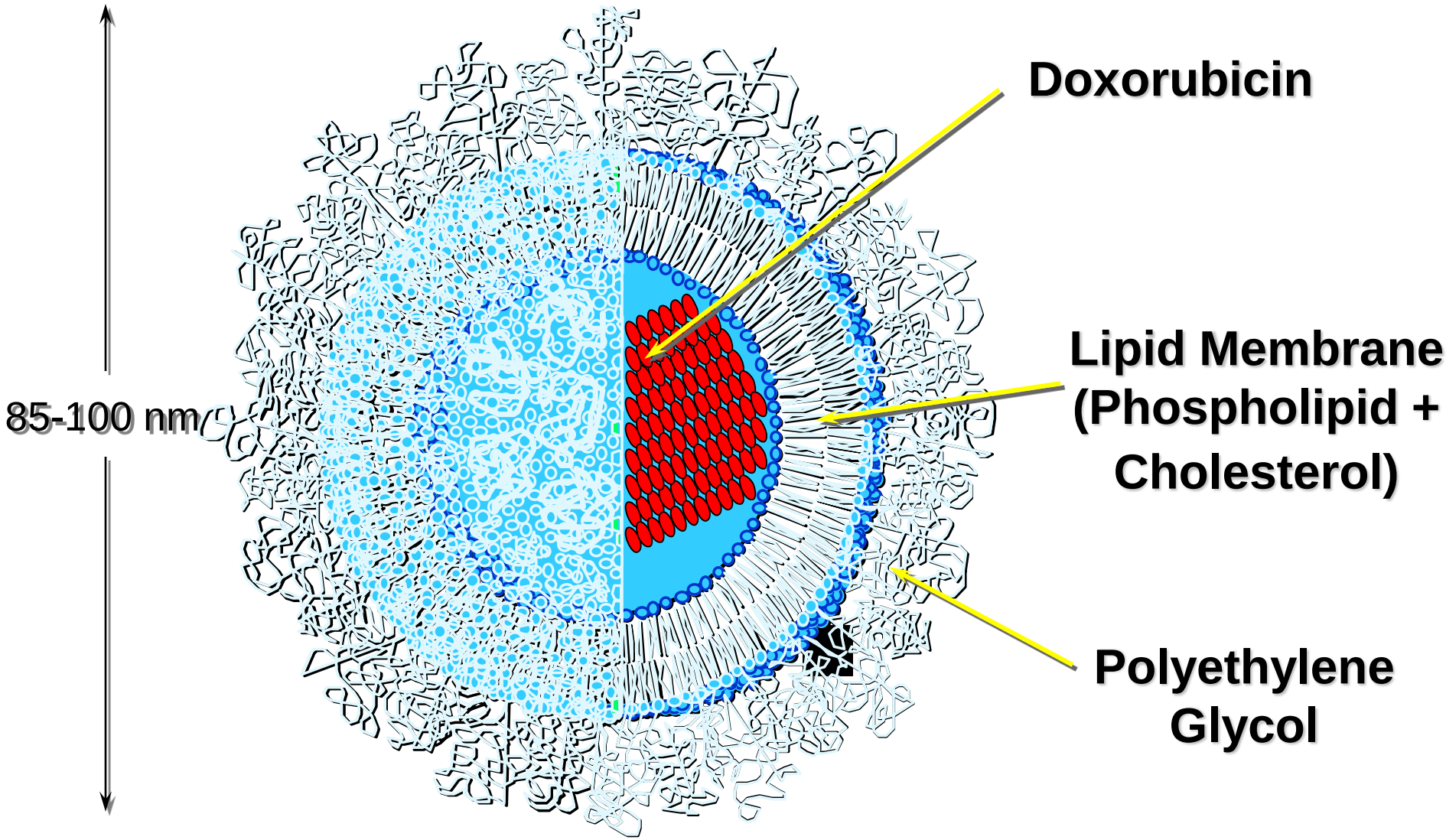
Bobo et al, Pharm Res (2016)

Approved Nanoparticulate Nanomedicines Only Liposome Drug Products

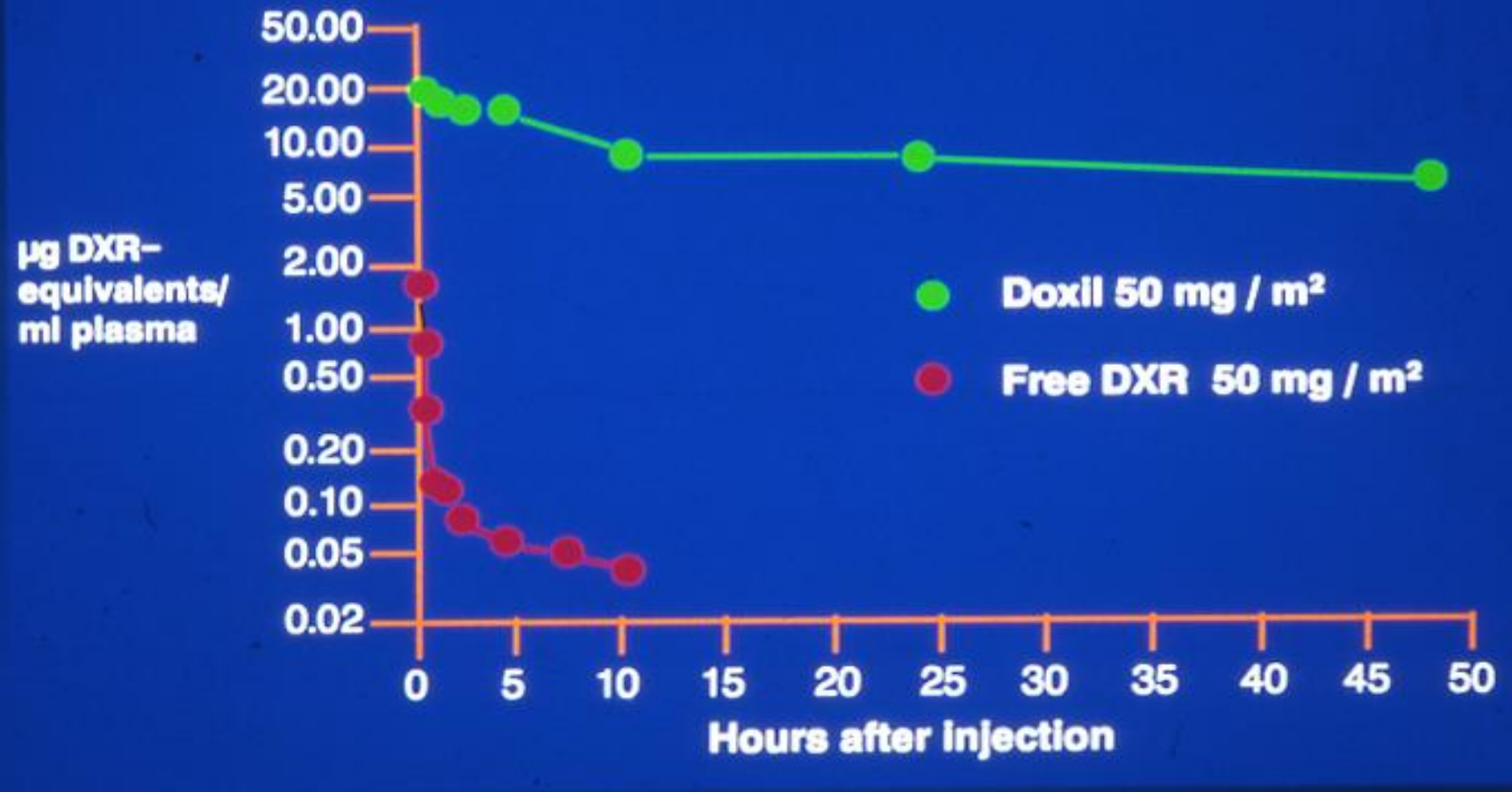
1. Doxil/Caelyx (doxorubicin)
2. Ambisome (amphotericin B)
3. DaunoXome (daunorubicin)
4. Myocet (doxorubicin)
5. Abelcet (amphotericin B)
6. Lipo-Dox (doxorubicin)
7. Marquibo = Onco-TCS (vincristine)
8. Onivyde (irinotecan)
9. CPX-351/Vyxeos (cytarabine/daunorubicin)
10. Arikayce (amikacin, inhalation product)

Reg: KS, ovariumkanker, borstkanker, myeloma

Structure of Doxil®



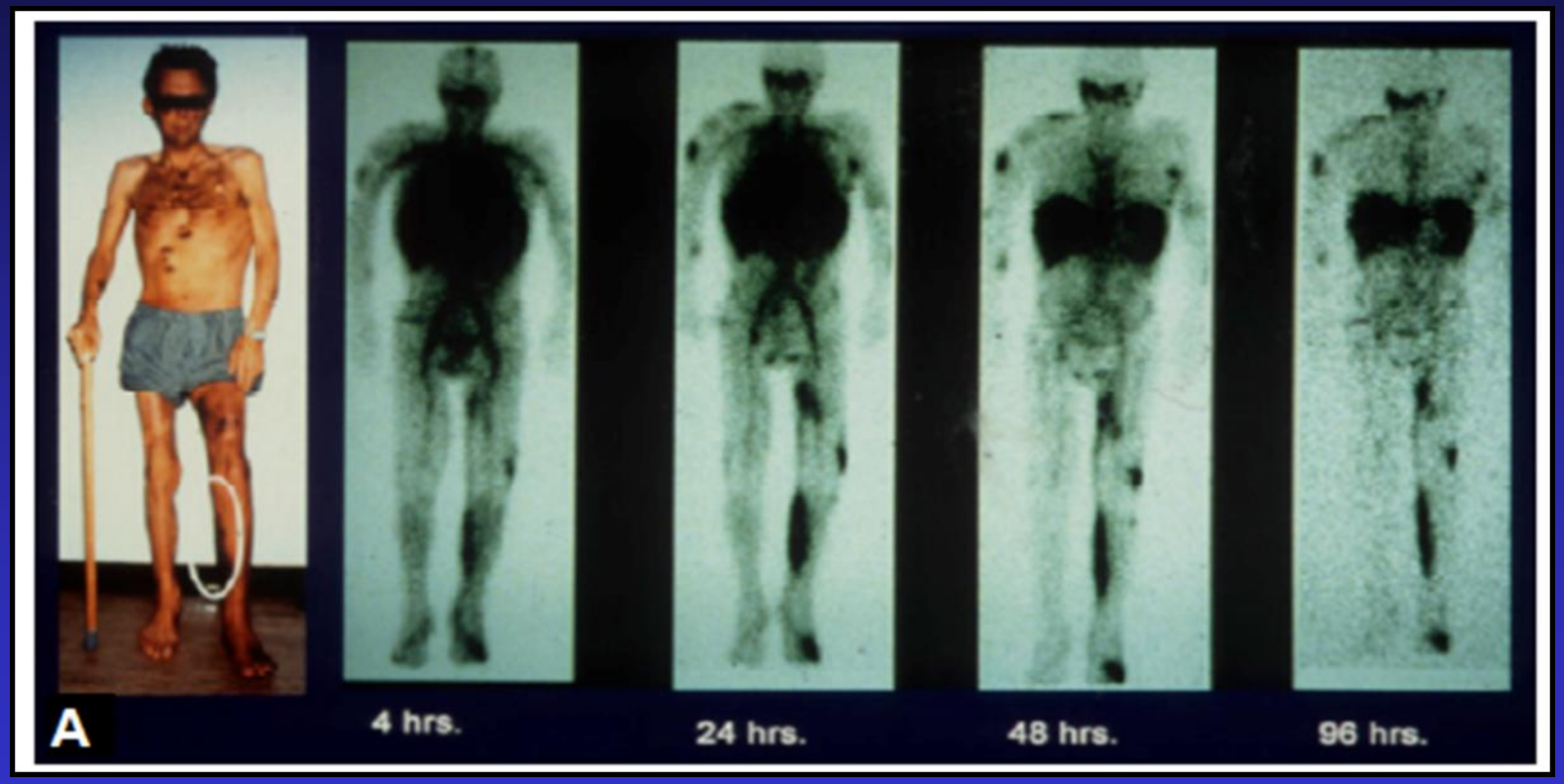
Clinical PK of DXR in LCL (PEG–HSPC–Chol)

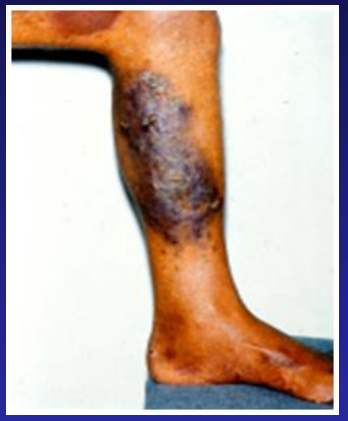


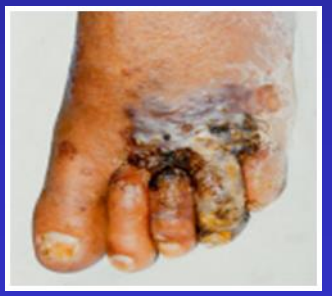
Gabizon et al.

Imaging EPR in patients

Harrington et al., Clin Cancer Res 2001







Doxil in Kaposi sarcoma : highly efficient EPR => highly efficient treatment

: 1 CR + 60/133 PR (46%) vs. ABV 31/125 PR (25%)

Doxil/Caelyx vs. free DOX

Like

Less risk of developing cardio-toxicity

	No. of patients[a]	
	PLD[b] (n = 254)	Doxorubicin[c] (n = 255)
Patients who developed cardiotoxicity (LVEF defined)	10	48
Cardiotoxicity (with signs and symptoms of CHF)	0	10
Cardiotoxicity (no signs and symptoms of CHF)	10	38
Patients with signs and symptoms of CHF only	2	2

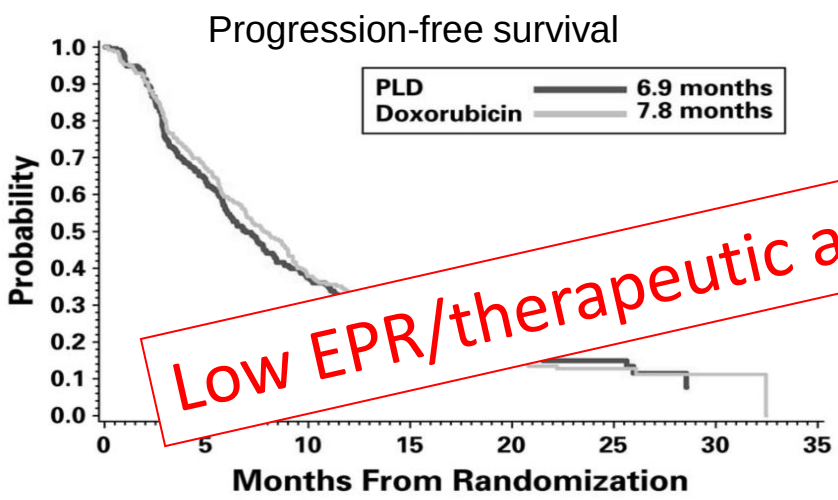
LVEF: left ventricular ejection fraction, CHF: congestive heart failure

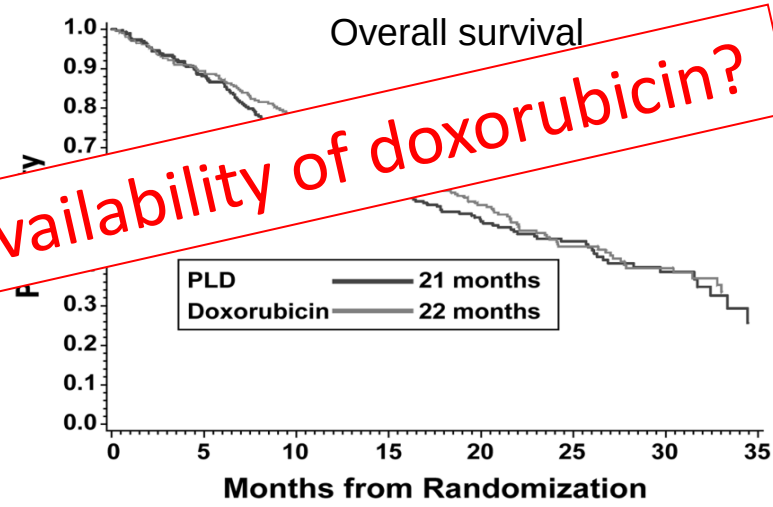
O'Brien, 2004, Ann. Oncol.:

- *Phase III trial*
- *Pegylated liposomal doxorubicin vs. conventional doxorubicin*
- *Metastatic breast cancer*

Dislike

Comparable survival





Low EPR/therapeutic availability of doxorubicin?

Reason for Approval Doxil in 1995

Therapeutic Index increased:

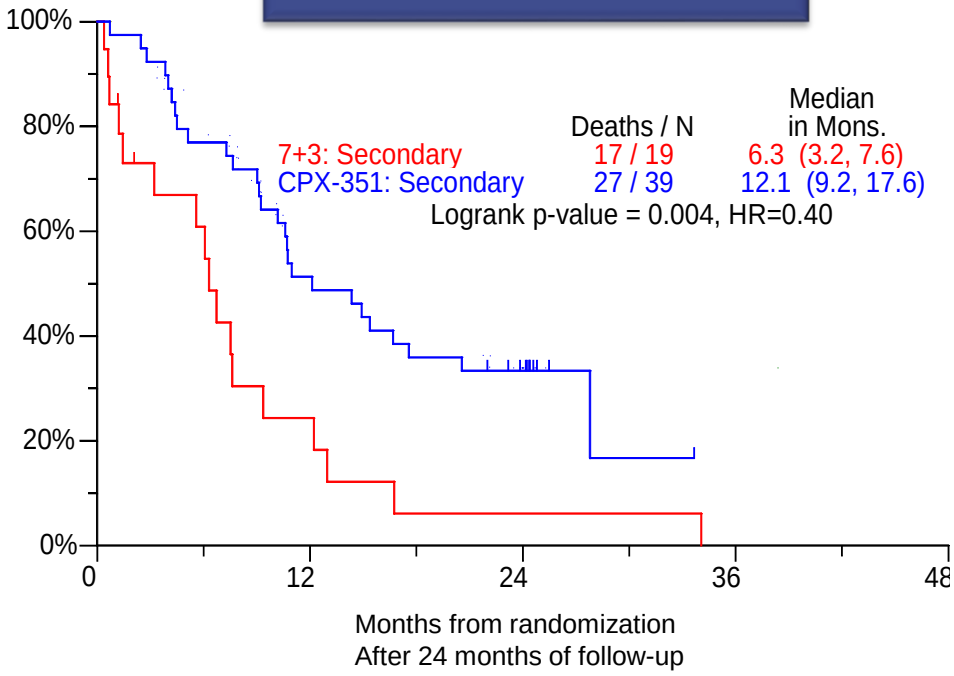
Efficacy / Toxicity

Targeted nanomedicines can favorably change the efficacy/safety balance

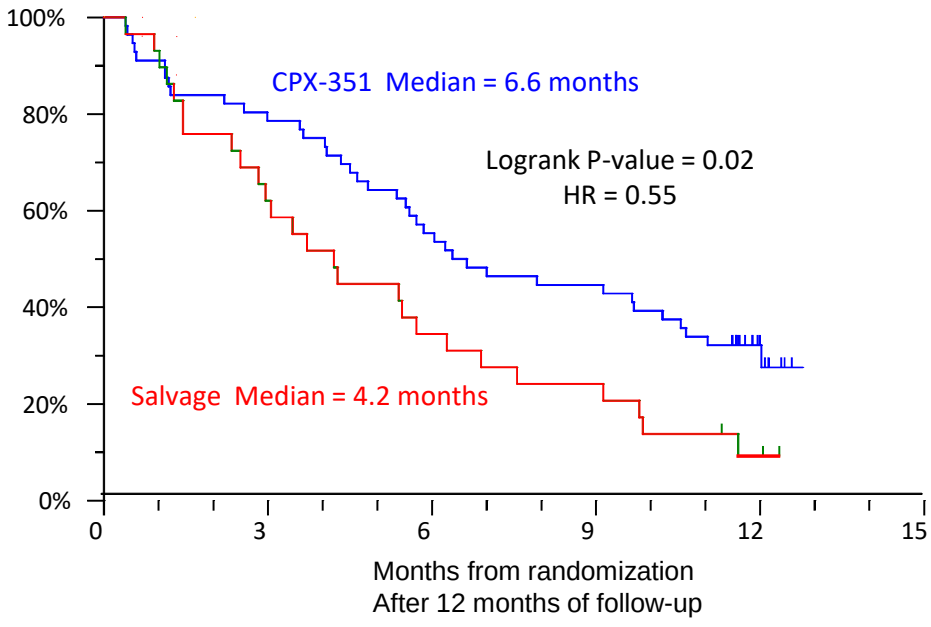
Study 204 & 205: Significant Improvement in Overall Survival for CPX-351 Treatment Seen in sAML and Unfavorable Risk – First Relapse AML

Overall Survival

Study 204 sAML
n=58 patients*



Study 205 Unfavorable Risk-First Relapse
n=85 patients



1 patient on the 7+3 arm was alive at 12 months after crossing over and responding to CPX-351 treatment

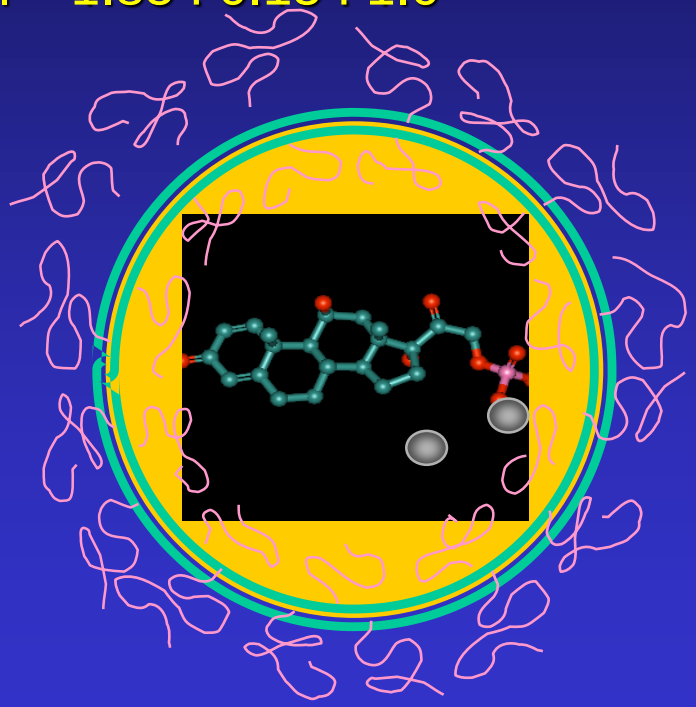
Liposomes in clinical trials (24)

- Lipoplatin (cisplatin)
- ThermoDox (doxorubicin)
- 9NC-LP (9-nitrocamptothecin)
- SPI-077 (cisplatin),
- Lipoxal(oxaliplatin)
- EndoTAG-1 (paclitaxel),
- OSI-211 (lutotecan),
- LE-DT (docetaxel),
- LEP-ETU (paclitaxel)
- TKM-080301
- PLK1(siRNA)
- Aru027, PKN3(siRNA)
- 2B3-101 (doxorubicin)
- MTL-CEBPA (CEBPA siRNA)
- TL1 (topotecan)
- IHL-305 (irinotecan)
- ATI-1123 (docetaxel)
- Alocrest (vinorelbine)
- LiPlaCis (cisplatin)
- MCC-465 (doxorubicin)
- SGT-53 (p53 gene)
- Nanocort (prednisolone)
- RNL (Image-guided delivery of rhenium nanoliposome)
- Patisiran (siRNA)

glucocorticoids encapsulated in PEG-liposomes

properties of initial preparation:

- lipid bilayer composition: DPPC : PEG-DSPE : Chol = 1.85 : 0.15 : 1.0
- size: diameter ± 90 nm
- glucocorticoid: prednisolone phosphate
- encapsulation efficiency: 3 - 4 %
- 1 ml preparation contains (on an average):
  - 50 mg (60 µmol) total lipid
  - 4 mg prednisolone-phosphate

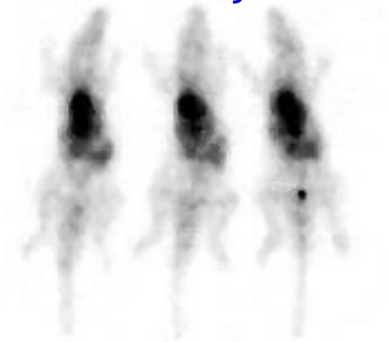


Target site accumulation in preclinical models

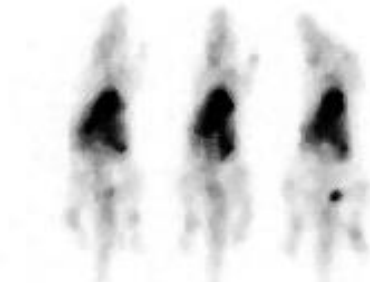
EPR effects are stronger
in case of
severe inflammation (vs. tumors)

preclinical results in rat arthritis: inflamed joint targeting

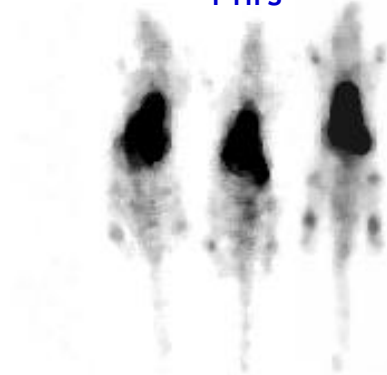
at time of injection



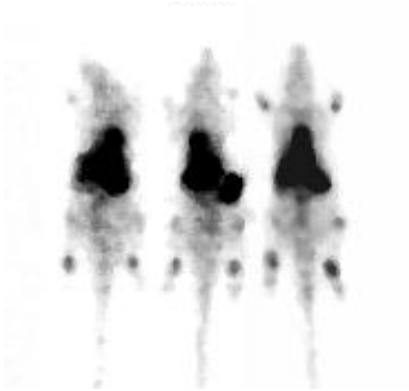
1 hr



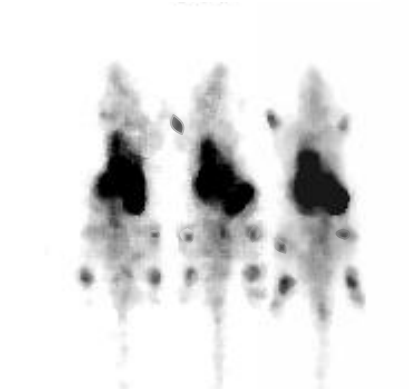
4 hrs



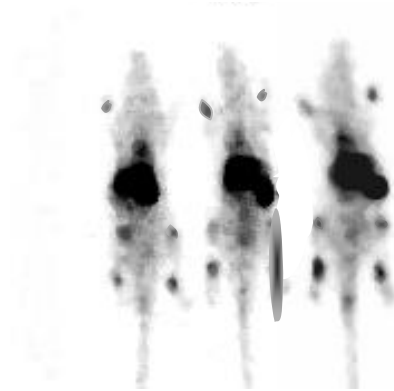
20 hrs



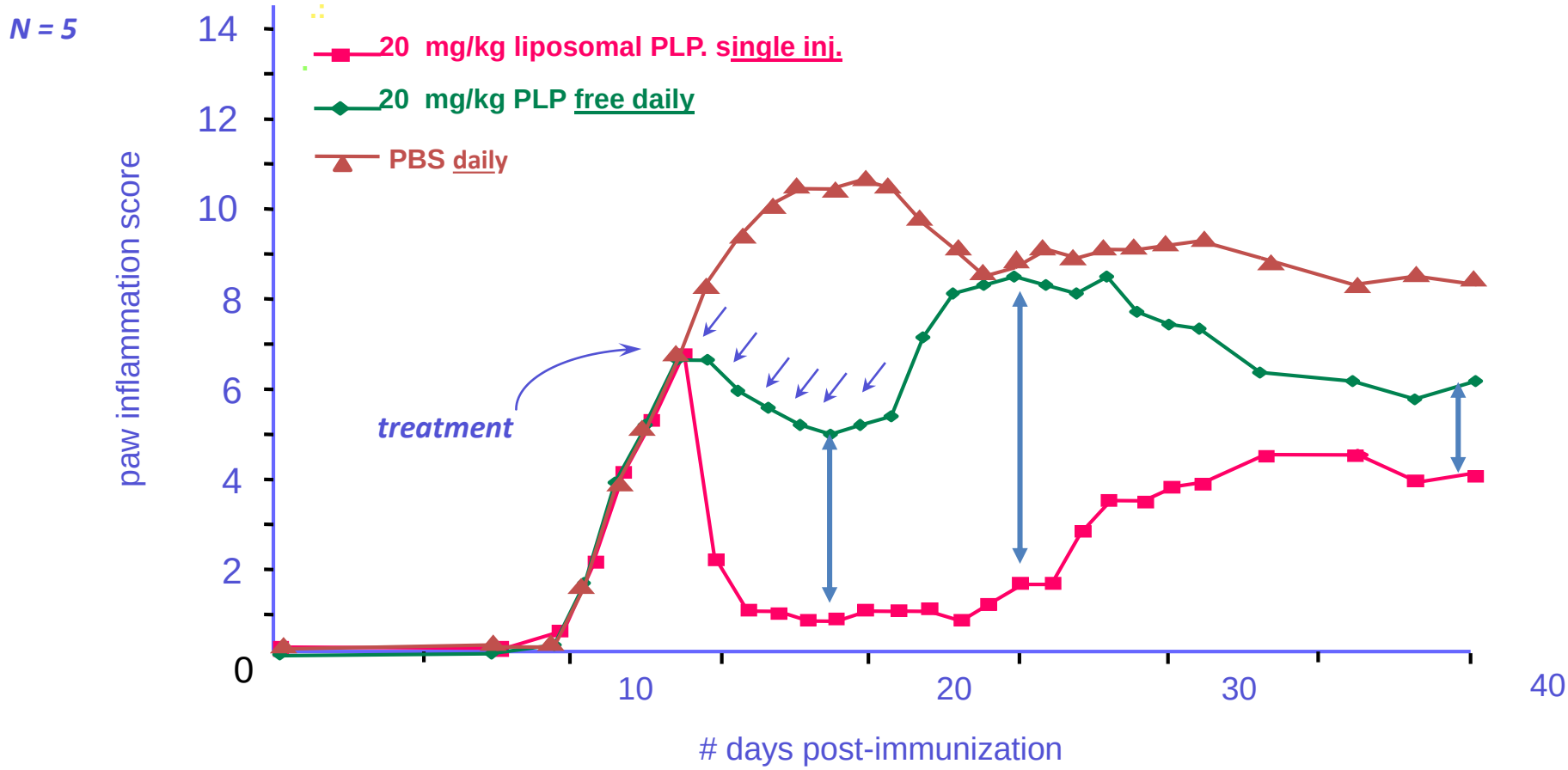
24 hrs



48 hrs

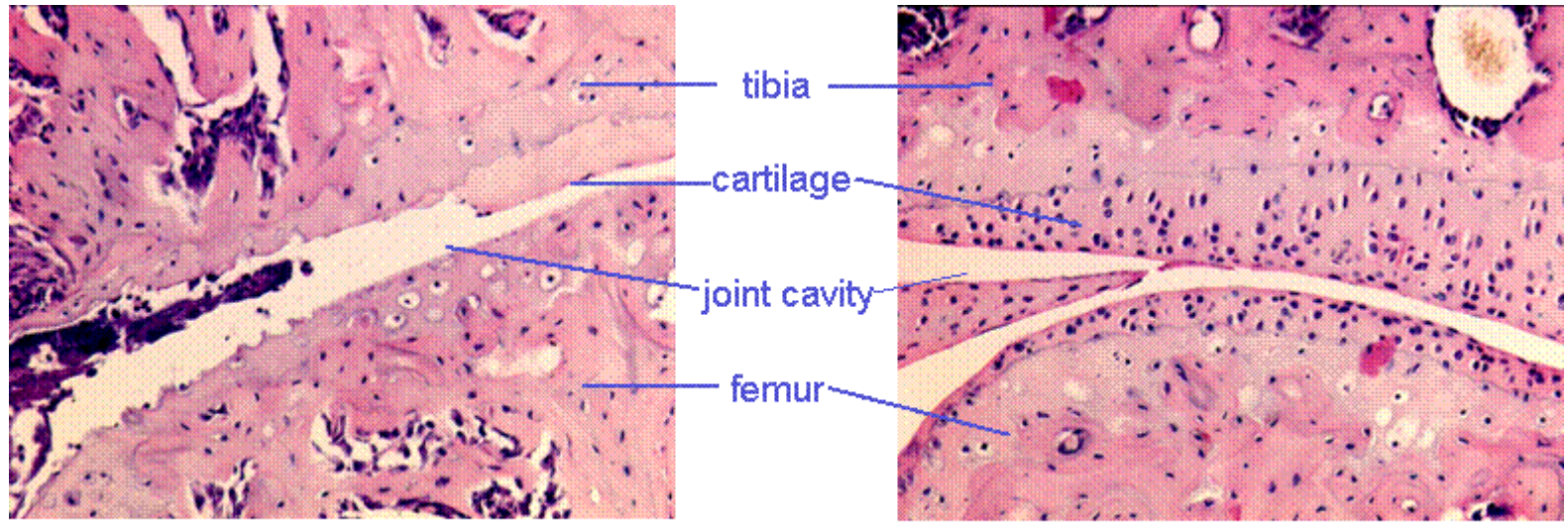


efficacy results Nanocort in rat arthritis:
rapid, intense and sustained



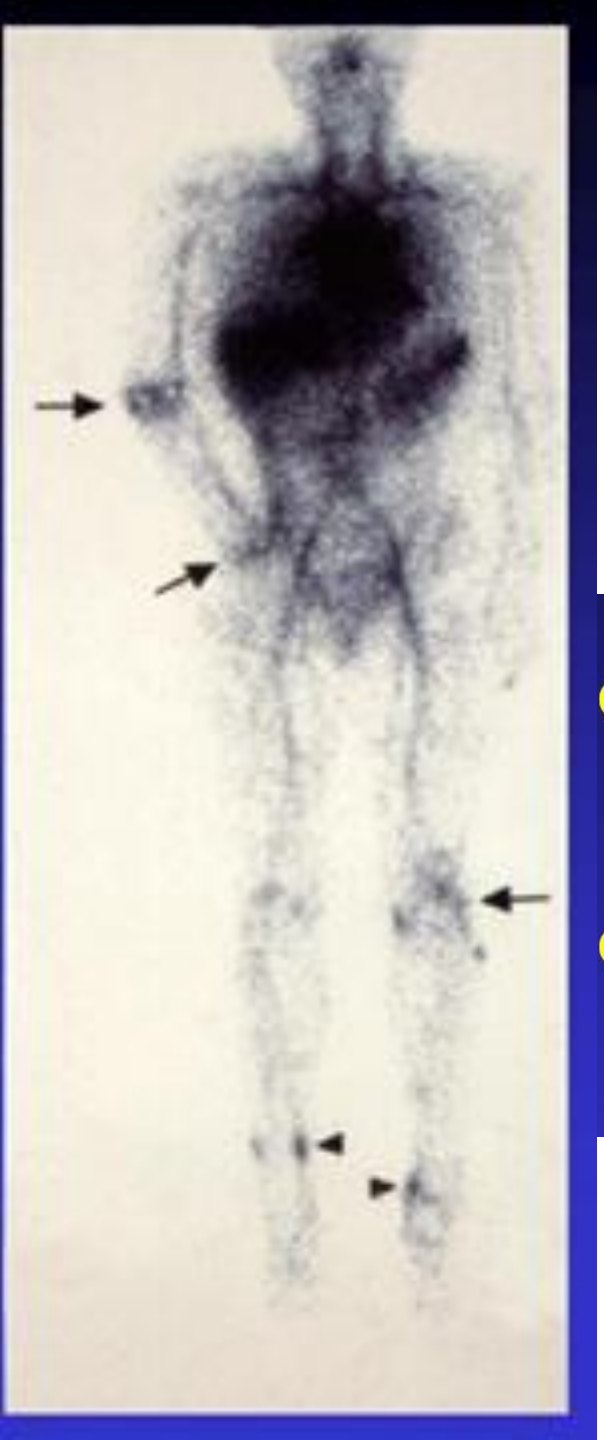
Mouse knee joint sections: effect on cartilage erosion

1 week after treatment



enceladus

when quenching the flares *... silence the tyrant!*



Imaging of inflamed joint targeting in humans

^{99m}Tc - labeled PEG-liposomes

whole body scintigraphy at 24 hr p.i.

- long circulation time of liposomal nanoparticles (by coating with PEG)
- stability in bloodstream: no release of incorporated drug

Disease indications that we pursue with clinical studies

Nanocort (i.v. pegylated liposomal prednisolone phosphate)

- Rheumatoid Arthritis
- Multiple Sclerosis
- Atherosclerosis
- Arteriovenous Fistula failure
- Inflammatory Bowel Disease (Most recent result: 70% response rate)

Oncocort (i.v. pegylated liposomal dexamethasone phosphate)

- Advanced Prostate Cancer (bone metastasis)
- Multiple Myeloma

Innovicort (i.v. pegylated liposomal triamcinolone acetonide phosphate)

- Uveitis (together with SNEC hospital Singapore)

Liposomes in clinical trials (24)

- Lipoplatin (cisplatin)
- ThermoDox (doxorubicin)
- 9NC-LP (9-nitrocamptothecin)
- SPI-077 (cisplatin),
- Lipoxal(oxaliplatin)
- EndoTAG-1 (paclitaxel),
- OSI-211 (lutotecan),
- LE-DT (docetaxel),
- LEP-ETU (paclitaxel)
- TKM-080301
- PLK1(siRNA)
- Aru027, PKN3(siRNA)
- 2B3-101 (doxorubicin)
- MTL-CEBPA (CEBPA siRNA)
- TL1 (topotecan)
- IHL-305 (irinotecan)
- ATI-1123 (docetaxel)
- Alocrest (vinorelbine)
- LiPlaCis (cisplatin)
- MCC-465 (doxorubicin)
- SGT-53 (p53 gene)
- Nanocort (prednisolone)
- RNL (Image-guided delivery of rhenium nanoliposome)
- Patisiran (siRNA)

Examples of Cancer Nanomedicine Formulations in Clinical Development

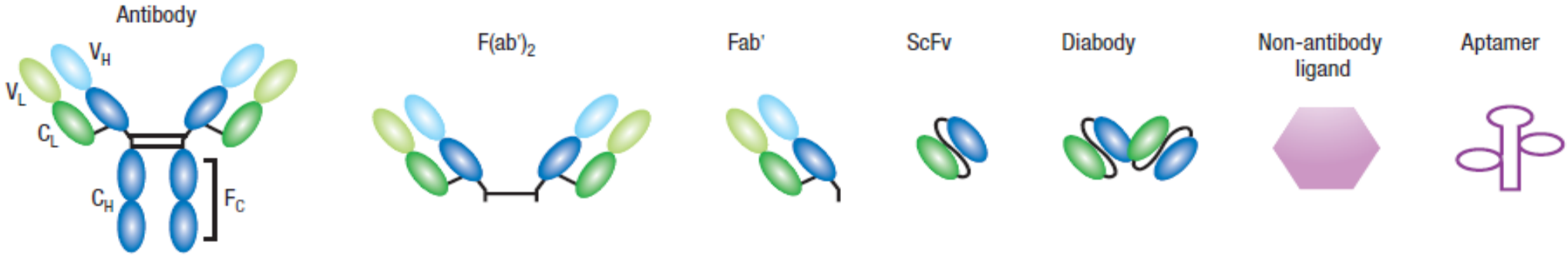
Nanoparticles (12): BA-003 (doxorubicin), DHAD-PBCA-NPs (mitoxantrone), BIND-014 (docetaxel), CRLX101 (camptothecin), IT-101 (camptothecin), Rexin-G (dnG1 pDNA), ABI-008 (docetaxel), ABI-009 (rapamycin), C-Visa-BikDD (BikDD pDNA), Nanoxel (paclitaxel), Docetaxel-NP (docetaxel), CALAA-01 (anti-RRM2 siRNA)

Polymer drug conjugates (9): Oncaspar (asparaginase), Xyotax (CT-2103) (paclitaxel), Taxoprexin (paclitaxel), PK1 (doxorubicin), PegAsys/PegIntron (IFN-alpha2a/b), ProLindac (oxaliplatin), AP 5346 (diaminocyclohexane platinum), DEP (docetaxel), XMT-1001 (CPT)

Antibody drug conjugates: most successful but often excluded from lists

- Passive targeting (- targeting ligand)
- Active targeting (+ targeting ligand)

Traditional targeting ligands



Peer *et al*., 2007, Nat Nanotechnol

Ligand-targeted particulate nanomedicines undergoing clinical evaluation

Lipid-based nanomedicines							
MBP-426	Mebiopharm	50–200	Oxaliplatin	Protein	Transferrin receptor	Metastatic gastric, gastro esophageal junction, esophageal adenocarcinoma	Phase II
SGT-53	SynerGene Therapeutics	90	p53 plasmid DNA	Antibody fragment (scFv)	Transferrin receptor	Solid tumors	Phase Ib
SGT-94	SynerGene Therapeutics	90	RB94 plasmid DNA	Antibody fragment (scFv)	Transferrin receptor	Solid tumors	Phase I
MM-302	Merrimack Pharmaceuticals	75–110	Doxorubicin	Antibody fragment (scFv)	ErbB2 (HER2)	Breast cancer	Phase I
Lipovaxin-MM	Lipotek		Melanoma antigens and IFNγ	Single domain antibody (dAb) fragment (VH)	DC-SIGN	Melanoma vaccine	Phase I
Anti-EGFR ILs-DOX	University Hospital Basel	85	Doxorubicin	Antibody fragment (Fab′)	EGFR	Solid tumors	Phase I
2B3-101	to-BBB Technologies		Doxorubicin	Protein	Glutathione transporters	Solid tumors	Phase I/IIa
MCC-465	Mitsubishi Pharma Corporation	140	Doxorubicin	Antibody fragment (F(ab)′2)	Not characterized	Advanced gastric cancer	Phase I (discontinued)
Polymer-based nanomedicines							
BIND-014	BIND Biosciences	100	Docetaxel	Small molecule	Prostate specific membrane antigen	Solid tumors	Phase II
CALAA-01	Calando Pharmaceuticals	50–70	RRM2 siRNA	Protein	Transferrin receptor	Solid tumors	Phase I
SEL-068	Selecta Biosciences	150–250	Nicotine antigen, T-helper cell peptide, TLR agonist	Small molecule	Antigen presenting cells	Smoking cessation vaccine	Phase I
Bacterially-derived minicell							
Erbitux®EDVs$_{PAC}$	EnGeneIC	400	Paclitaxel	Antibody	EGFR	Solid tumors	Phase II
Retroviral vector							
Rexin-G	Epeius Biotechnologies	100	Cytocidal dominant negative cyclin-G1 DNA construct	Small molecule	Collagen	Sarcoma, osteosarcoma, pancreatic cancer	Phase II[a]

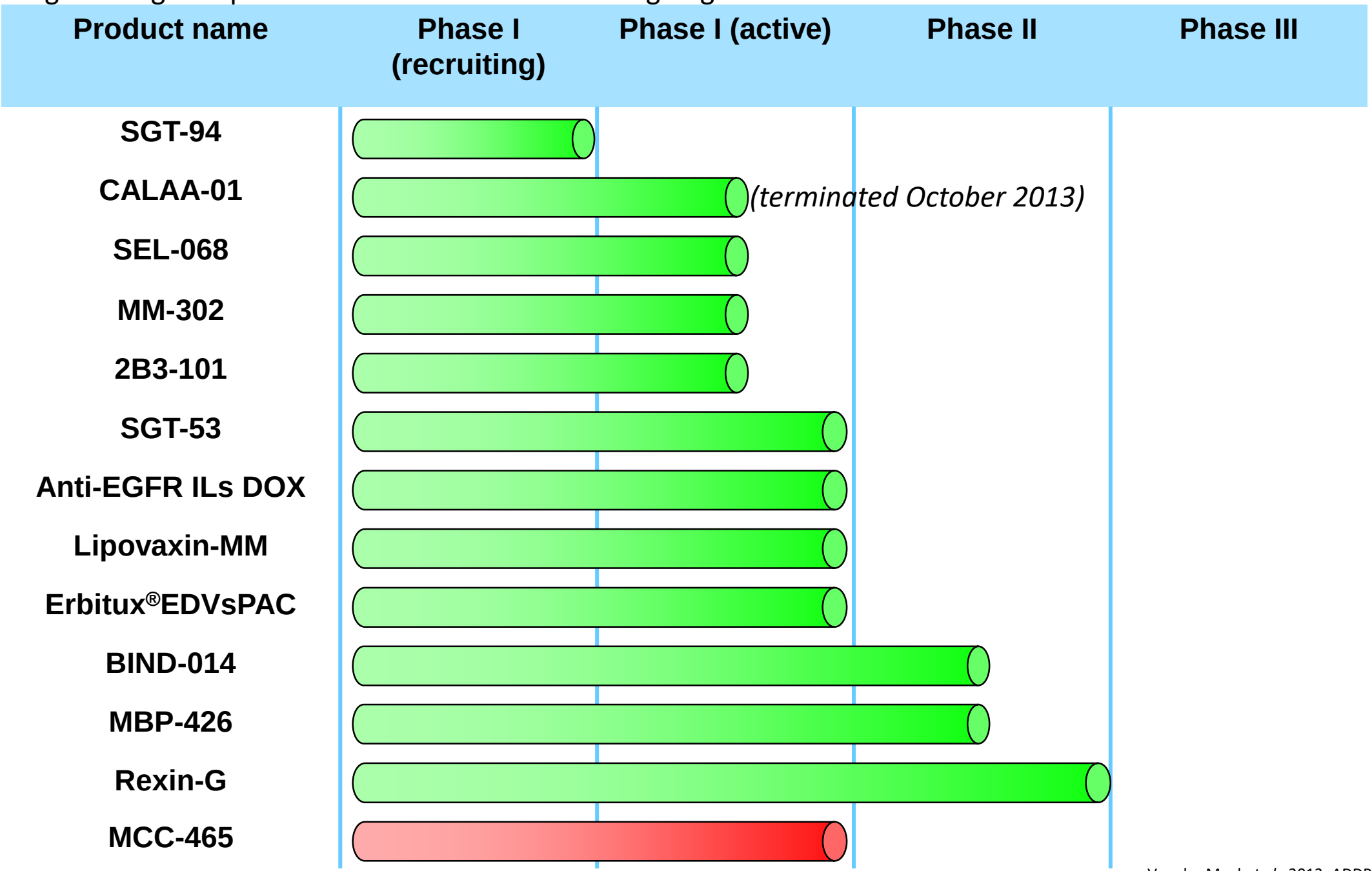
[a] Approved in the Republic of the Philippines under an expanded program as a first-line and adjuvant therapy for pancreatic and breast cancers, and as a second-line therapy for all chemotherapy-resistant solid malignancies.

Van der Meel *et al*., 2013, ADDR

Clinical Utility of Targeting Ligands

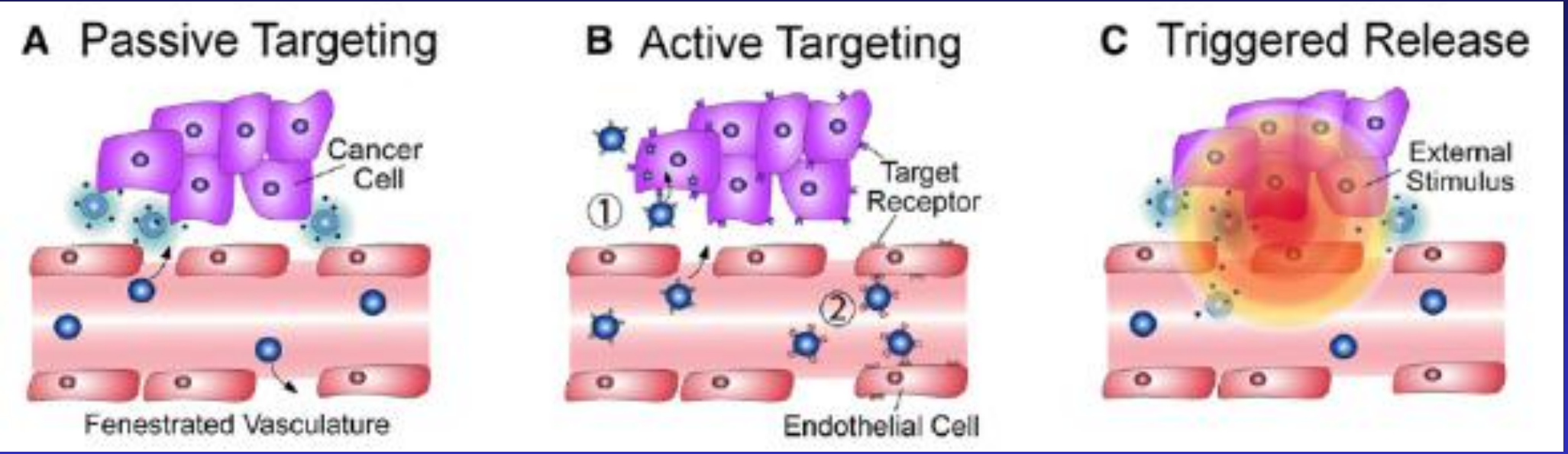
has NOT (yet) been unambiguously proven

Ligand-targeted particulate nanomedicines undergoing clinical evaluation



Van der Meel *et al*., 2013, ADDR

Main Drug Targeting Modes



Doxil/Caelyx vs. free DOX

Like

Less risk of developing cardio-toxicity

	No. of patients[a]	
	PLD[b] (n = 254)	Doxorubicin[c] (n = 255)
Patients who developed cardiotoxicity (LVEF defined)	10	48
Cardiotoxicity (with signs and symptoms of CHF)	0	10
Cardiotoxicity (no signs and symptoms of CHF)	10	38
Patients with signs and symptoms of CHF only	2	2

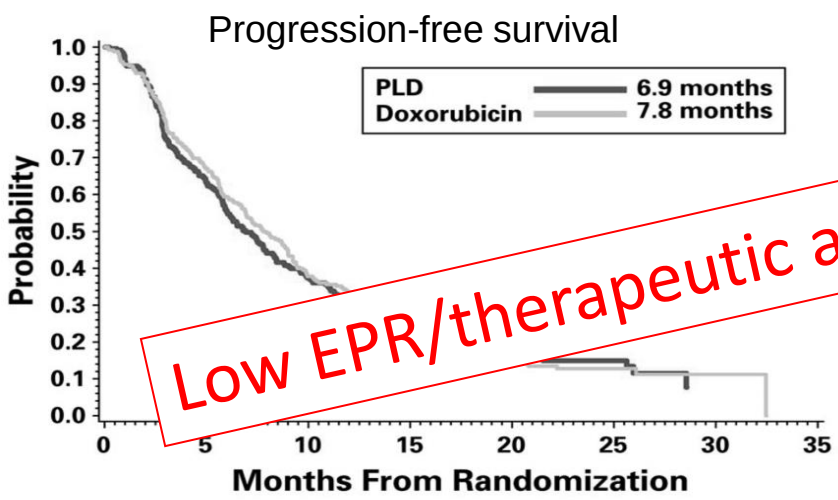
LVEF: left ventricular ejection fraction, CHF: congestive heart failure

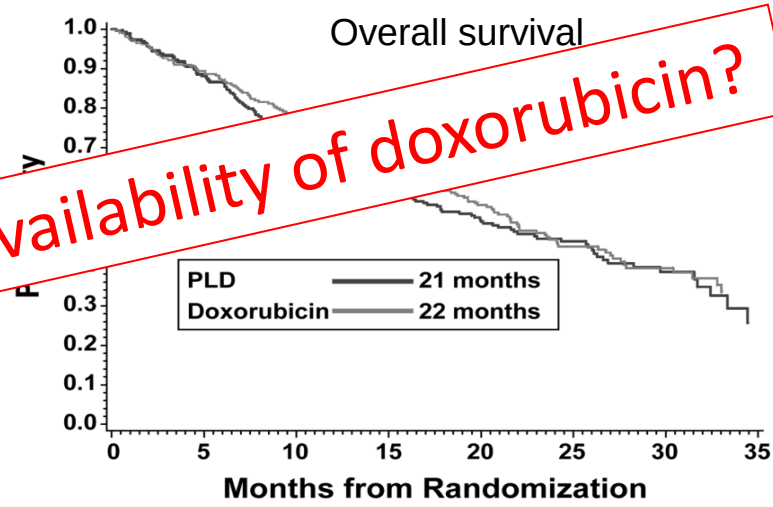
O'Brien, 2004, Ann. Oncol.:

- *Phase III trial*
- *Pegylated liposomal doxorubicin vs. conventional doxorubicin*
- *Metastatic breast cancer*

Dislike

Comparable survival





Low EPR/therapeutic availability of doxorubicin?

How to Improve Efficacy?

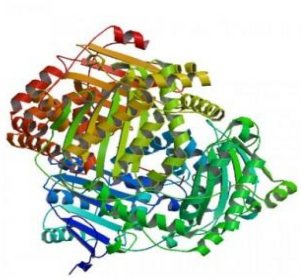
Influencing Major Efficacy Determinants:

- Improve Accessibility/EPR
  (e.g.vasodilators, hyperthermia)
- Enhance Intratumoral Drug Release

Solution: intratumoral triggered release

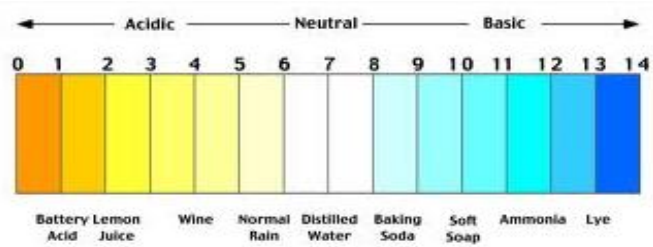
Use intrinsic or extrinsic stimulus to trigger release

Enzyme



Meers, 2001, ADDR

pH



Simões et al., 2004, ADDR

Temperature

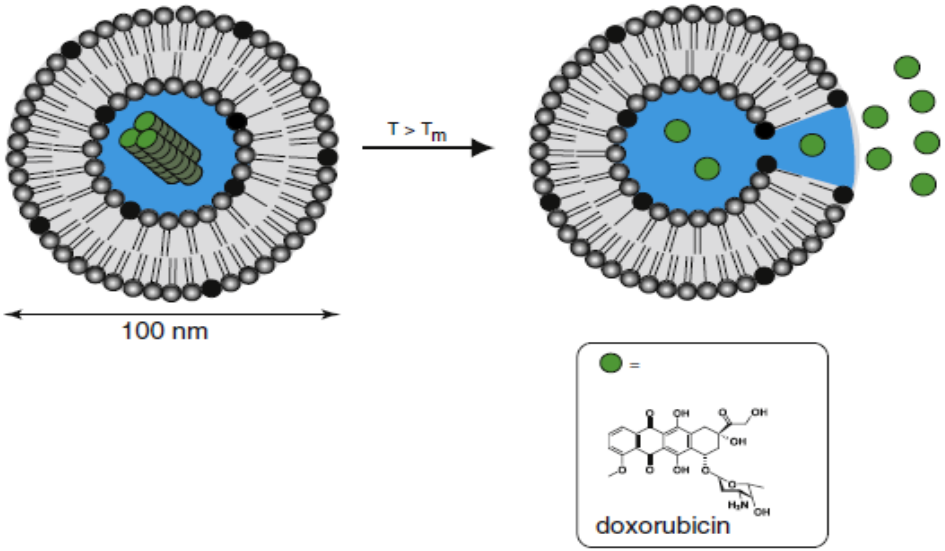
Grull et al., 2012, JCR

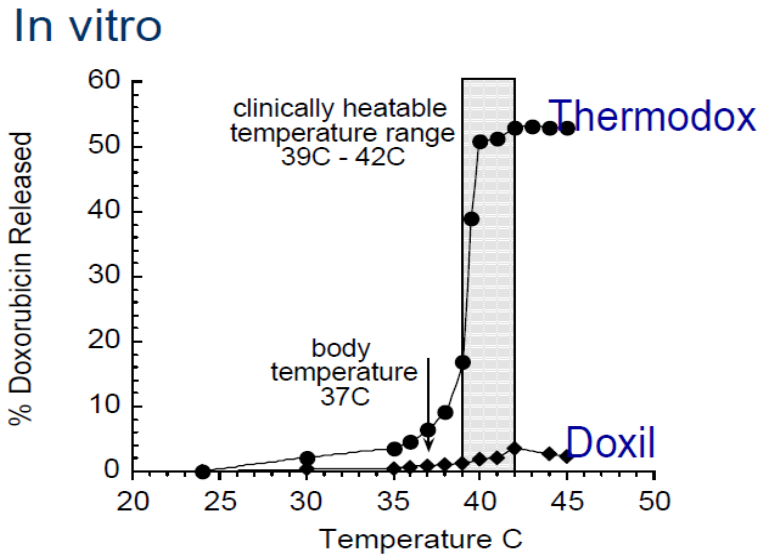
Light

You et al., 2010, ACS Nano

HIFU-triggered drug delivery from ThermoDox

No need for EPR!

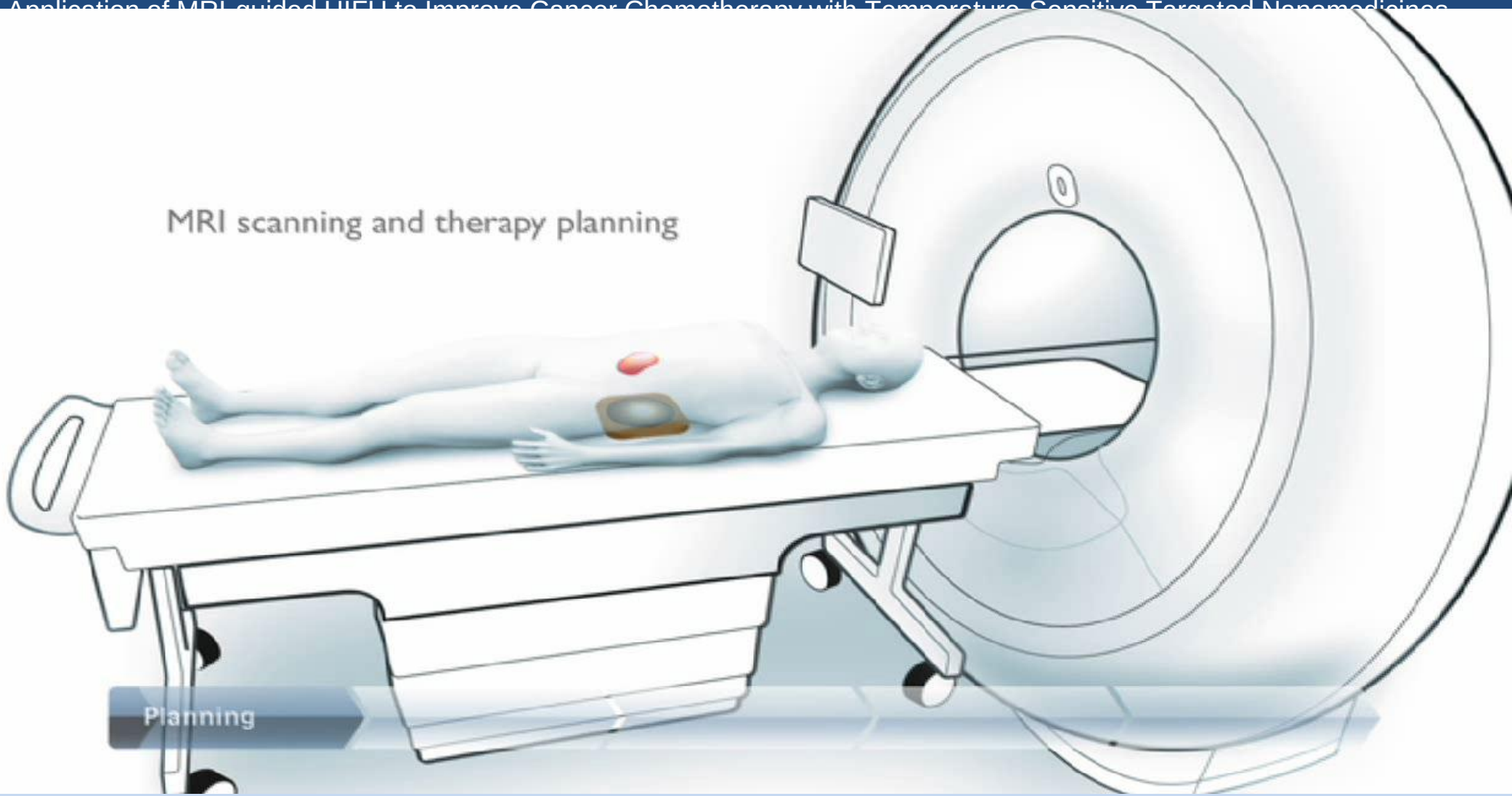




hifu-chem
a ctmm project

Center for Translational Molecular Medicine

Application of MRI-guided HIFU to Improve Cancer Chemotherapy with Temperature-Sensitive Targeted Nanomedicines



Real-time Monitoring of Intravascular Triggered Drug Release by ThermoDox

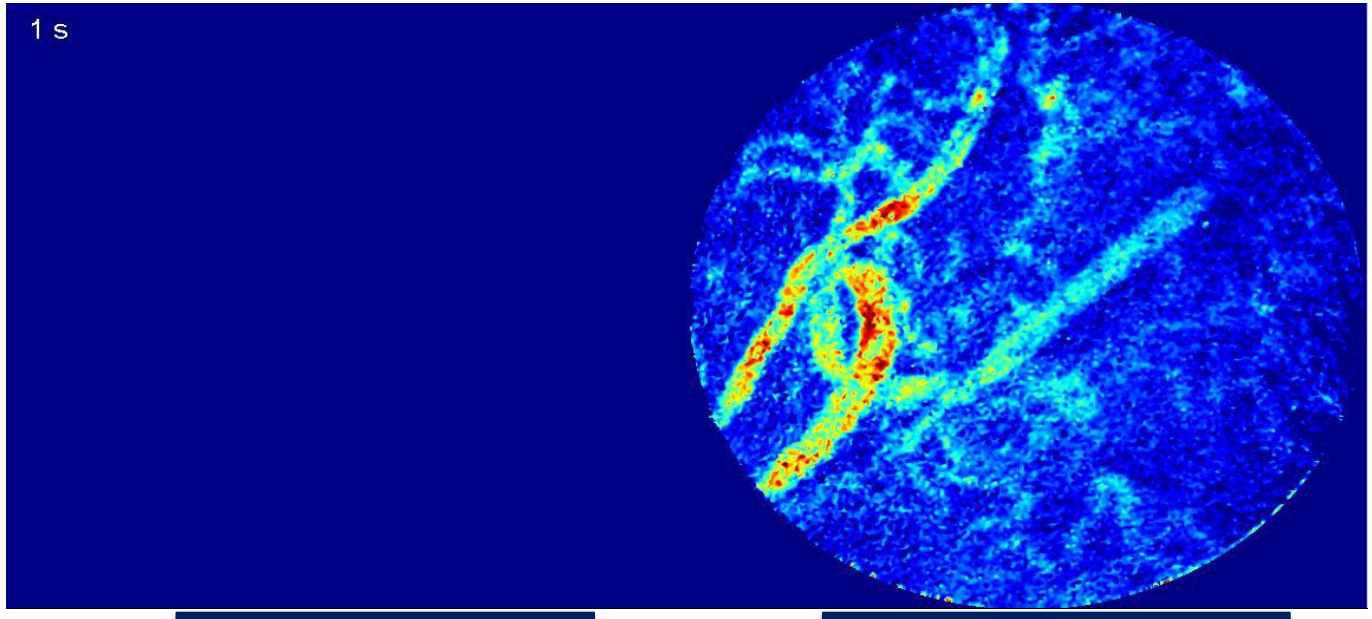
Marc Derieppe

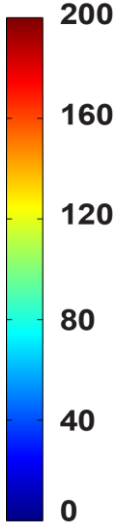
Prof. Chrit Moonen

University Medical Center Utrecht
The Netherlands

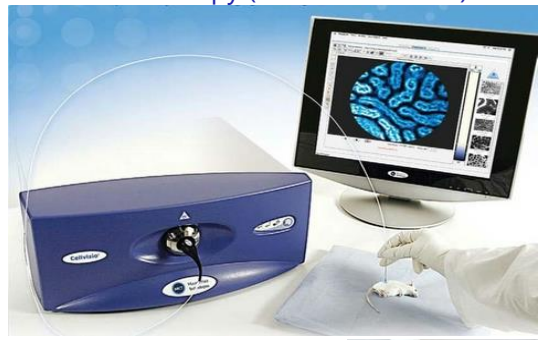
Thermodox bolus injection: 10" to 50"

Field of view: 600x600 microns



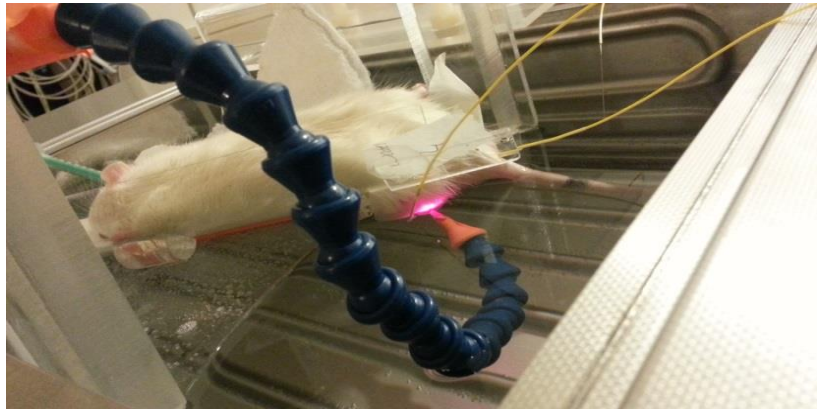


Fibered-based Confocal Fluorescence Microscopy (Mauna Kea Tech)



Diameter: 1.5 mm
(mini-invasive,
skin contact only)

Waterbath constantly at 43 C



488 nm — Native Doxorubicin fluorescence — 500 - 630 nm

660 nm — AngioSense® 680EX Blood vessel staining — 680 - 800 nm

Animal Model

- Wistar rats
- Rat subcutaneous rhabdomyosarcoma tumor in hind limb

Drug

- Thermodox® (Celsion Corp., USA)
- Phase transition temperature: 42 C
- Clinical dose injected intravenously: 4 mg/kg

Derieppe *et. al.* 2015, European Molecular Imaging Meeting

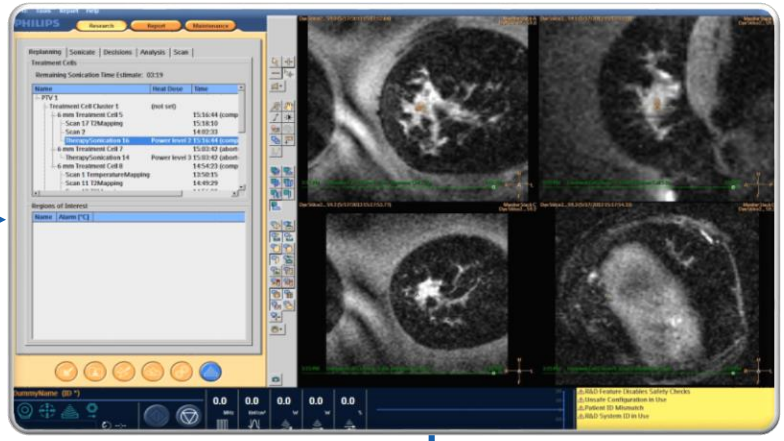
MR guided High Intensity Focused Ultrasound

MR with integrated HIFU

Image Guided Therapy 3D Planning

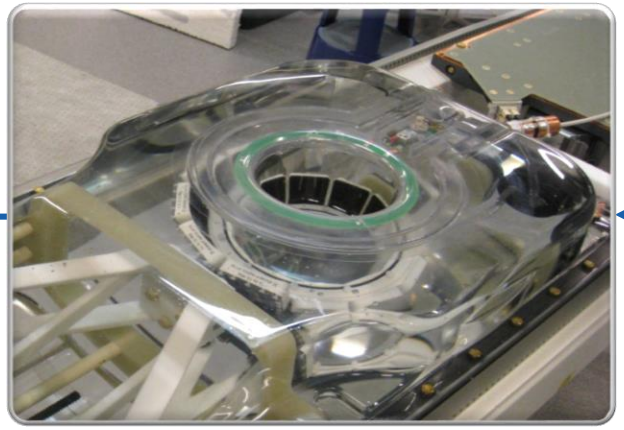
Temperature monitoring

Therapy Console



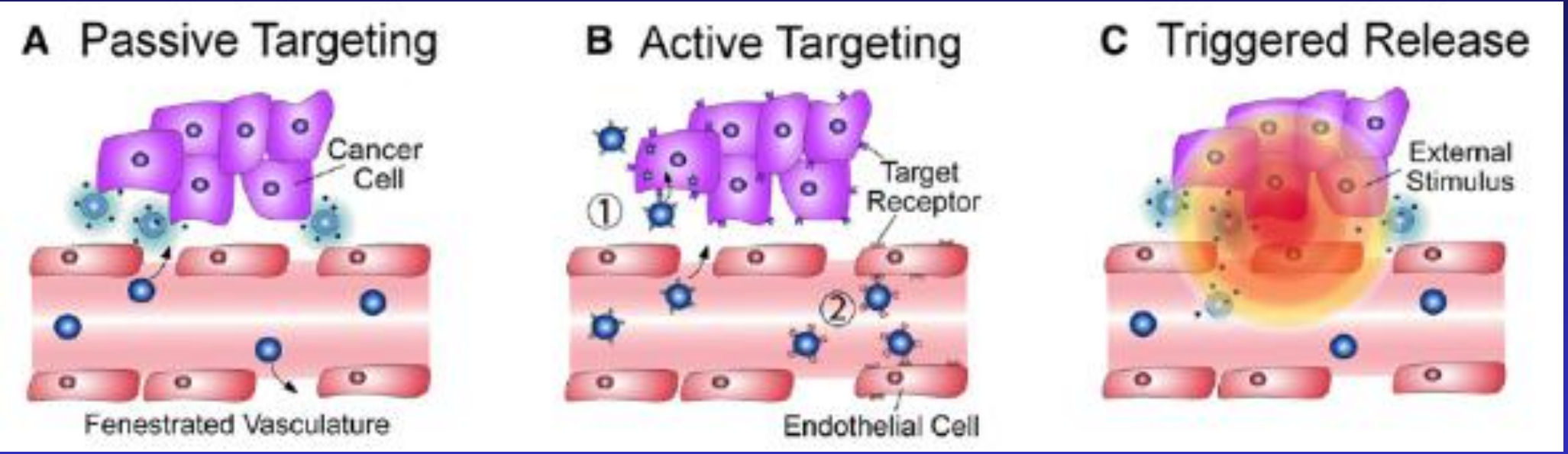
Real-time control

Ultrasound Transducer



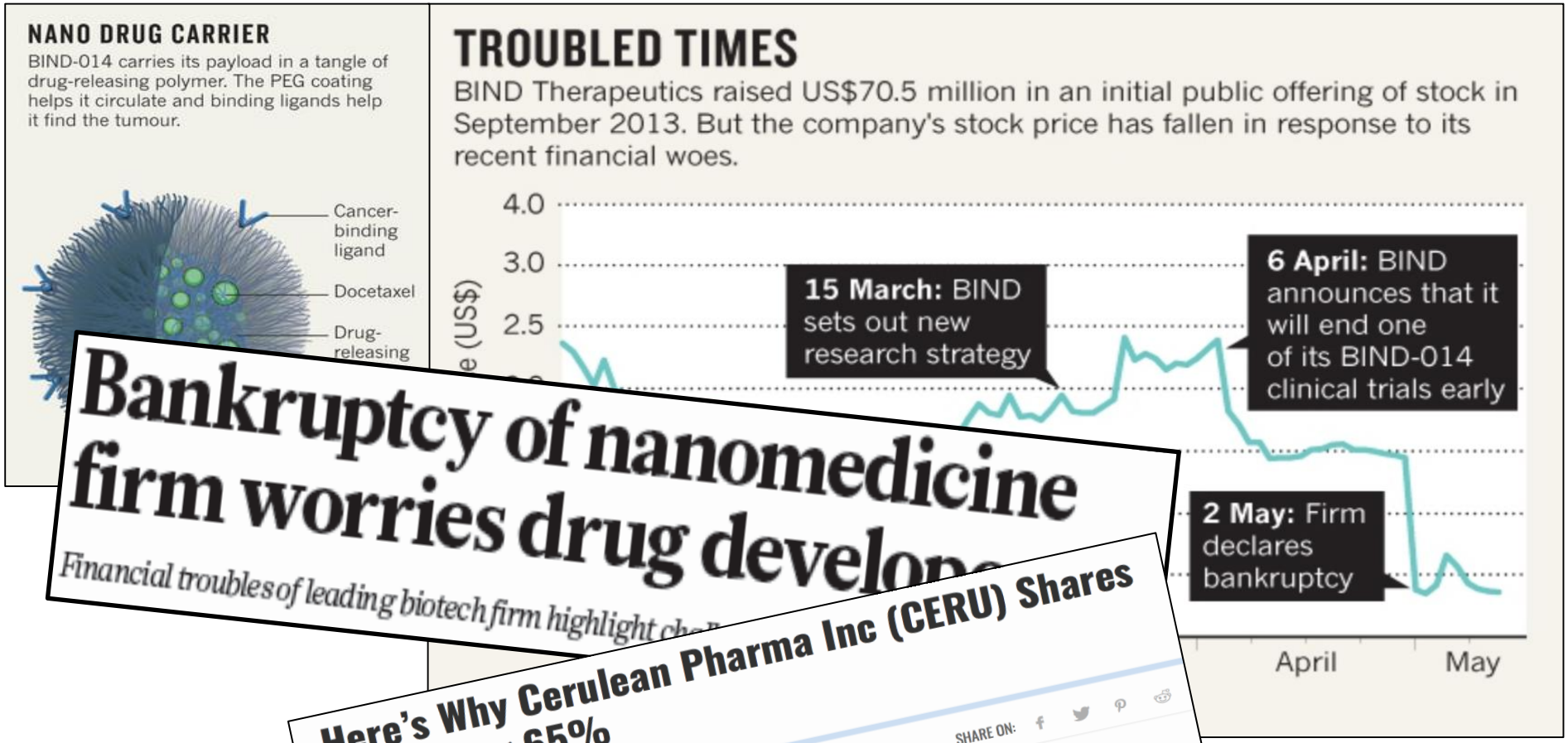
Thermal ablation & mild hyperthermia

Main Drug Targeting Modes



Wave of disappointment

2016 : Annus horribilis



Bankruptcy of nanomedicine firm worries drug develop

Financial troubles of leading biotech firm highlight ch

Here's Why Cerulean Pharma Inc (CERU) Shares Are Falling 65%

SHARE ON:

Corey Williams - March 20, 2017, 10:22 AM EDT

Shares of Cerulean Pharma Inc (NASDAQ:CERU) collapsed this morning, down nearly 65%, after investors learned that the company has sold certain assets for $7.5 million in conjunction with a stock purchase deal with Daré Bioscience.

CERULEAN
LEADERSHIP IN NANOPHARMACEUTICALS

Slide courtesy: Christine Allen

Year 2016 examples

Journal of Controlled Release 244 (2016) 108–121

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/jconrel

Review article

To exploit the tumor microenvironment: Since the EPR effect fails in the clinic, what is the future of nanomedicine?

F. Danhier

Université catholique de Louvain, Louvain Drug Research Institute, Advanced Drug Delivery and Biomaterials, Avenue Mounier, 73 bte B1 73.12, 1200 Brussels, Belgium

In the Abstract..

- "The basic rationale of the design and development of nanomedicines in cancer therapy is failing.."
- "The EPR effect works in rodents not in humans."
- "It is probably time to dethrone the EPR effect.."

nature REVIEWS MATERIALS

Analysis of nanoparticle delivery to tumours

Stefan Wilhelm, Anthony J. Tavares, Qin Dai, Seiichi Ohta, Julie Audet, Harold F. Dvorak and Warren C. W. Chan

Abstract | Targeting nanoparticles to malignant tissues for improved diagnosis and therapy is a popular concept. However, after surveying the literature from the past 10 years, only 0.7% (median) of the administered nanoparticle dose is found to be delivered to a solid tumour. This has negative consequences on the translation of

(Wilhelm et al, Nat Rev Mater 2016)

In the Abstract..

- "..after surveying the literature from the past 10 years, only 0.7% (median) of the administered nanoparticle dose is found to be delivered to a solid tumour."
- "This has negative consequences on the translation of nanotechnology for human use.."
- "We .. present a 30-year research strategy to overcome this fundamental limitation."

Journal of Controlled Release xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/jconrel

The drug delivery field at the inflection point: Time to fight its way out of the egg

Kinam Park[a,b,*]

[a] Purdue University, Department of Biomedical Engineering, West Lafayette, IN 47907, USA
[b] Purdue University, Department of Pharmaceutics, West Lafayette, IN 47907, USA

ARTICLE INFO

Keywords:
Nano-sized drug delivery systems
Nanoformulations
Clinical trials
Inflection point
Inconvenient truth
Advantage of nanoformulations
Limitations of nanoformulations
Future of drug delivery

ABSTRACT

The world is becoming a better place, in part, by breakthrough findings by scientists. In the drug delivery field, many breakthrough formulations have been achieved helping patients deal with various diseases effectively. The recent progress, however, has been slowing down, and many important drug delivery problems have not been resolved. They can be overcome by understanding the causes and finding the remedies. For the last three decades, the field has been overwhelmed by nanotechnology, nanomedicine, and many nano-sized drug delivery systems. Disappointing outcomes of nano-sized formulations (nanoformulations) in clinical studies indicate that our overall approach of nanomedicine needs serious reevaluation. The limited advantages of nanoformulations were drastically exaggerated, and the assumptions used in nanomedicine and nanoformulations turned out to be inapplicable to clinical applications. The drug delivery field is at the strategic inflection point, and we all have to face the reality by absorbing the inconvenient truth and fight our way out of the egg to break the ill-conceived illusion of nanomedicine. Scientists are proud of their independent thinking and their work that can change the world, but the current climate does not allow them to be true scientists. The future of the drug delivery field depends on how effectively we can find talented young scientists with motivation, cultivate them with resources, provide them with an environment for the free exchange of ideas, and nurture them with purpose, passion, and the conviction of doing meaningful science.

Some Quotes

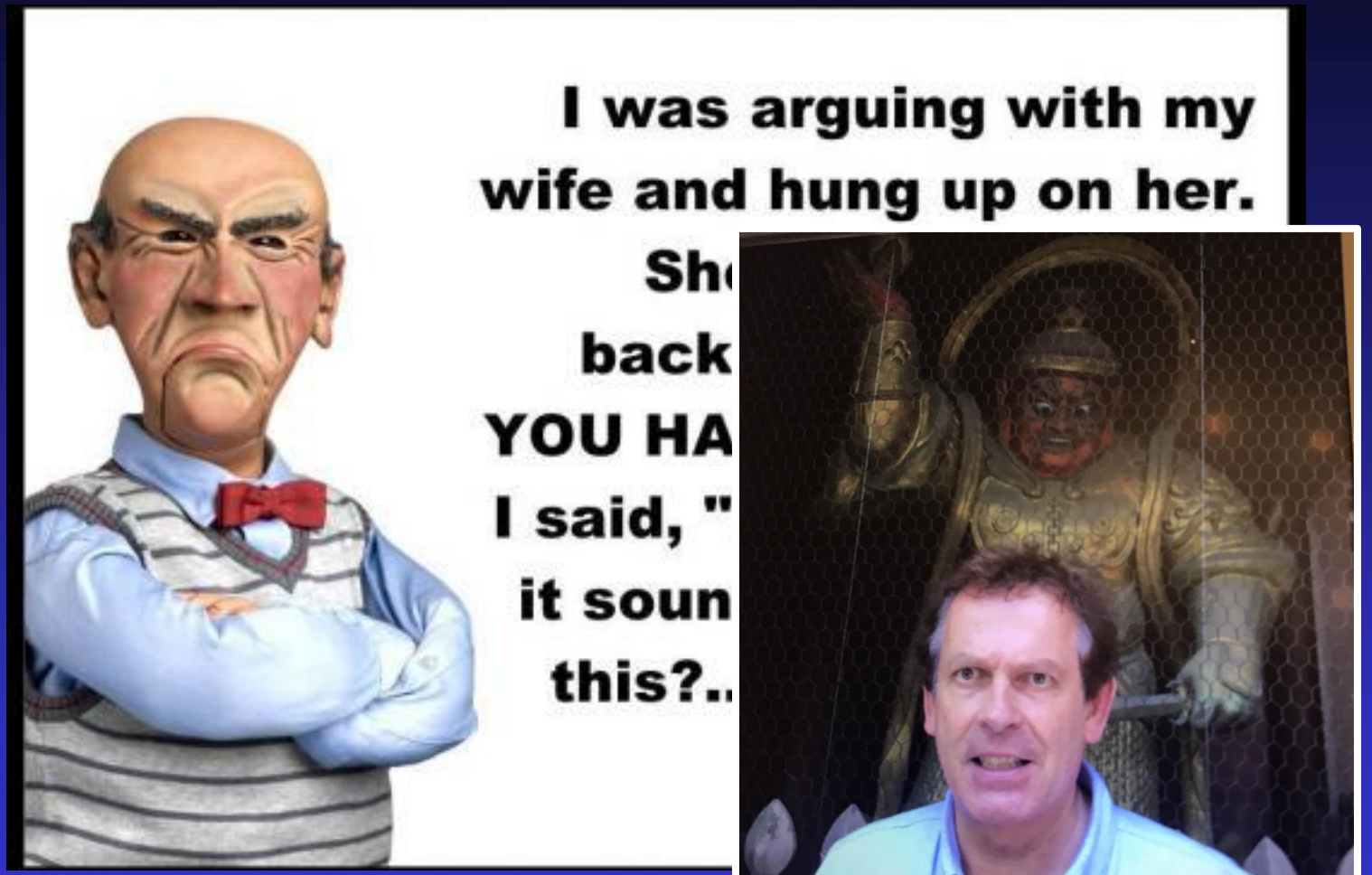
.. overall outcome of the nanomedicine field is a fatal failure.

.. assumptions used in nanomedicine and nanoformulations turned out to be inapplicable to clinical applications.

.. absorb the inconvenient truth .. to break the ill-conceived illusion of nanomedicine.

.. EPR effect is nothing more than trying to see a pattern when it is simply a random phenomenon.

.. spend the next few decades reshaping the field with a new generation of scientists with new ideas and new research tools.


I was arguing with my
wife and hung up on her.
Sh
back
YOU HA
I said, "
it soun
this?..

Wave of disappointment warranted?

Nanoparticles and Drug Targeting: Should we be disappointed?

- Setting the ‘debate’
- 0.7%ID tumor accumulation
- Tumor targeting via EPR
- Present and future

nature REVIEWS MATERIALS

Analysis of nanoparticle delivery to tumours

Stefan Wilhelm, Anthony J. Tavares, Qin Dai, Seiichi Ohta, Julie Audet, Harold F. Dvorak and Warren C. W. Chan

Abstract | Targeting nanoparticles to malignant tissues for improved diagnosis and therapy is a popular concept. However, after surveying the literature from the past 10 years, only 0.7% (median) of the administered nanoparticle dose is found to be delivered to a solid tumour. This has negative consequences on the translation of

(Wilhelm et al, Nat Rev Mater 2016)

INTUITION OF REALITY

ADHYĀTMA PRAKĀSHA KĀRYĀLAYA
HOLENARSIPUR
(Hassan District, Karnataka State)
PIN Code No. 573 211

Antibody-based therapy of solid cancer

- Clinically and commercially successful

  -annual sales: about 20 billion USD for solid tumour therapy alone

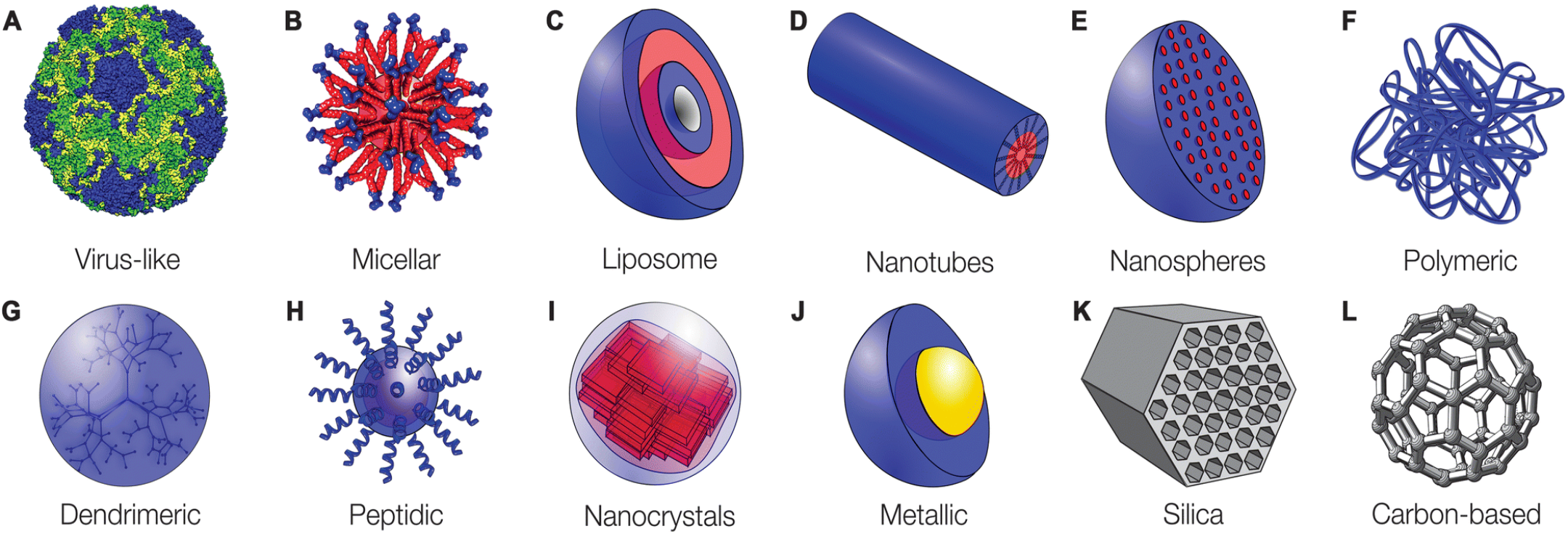
  - examples: the antibody drug conjugates Kadcyla (trastuzumab emtansine) and Adcetris (brentuximab vedotin)

- Antibodies do not target tumours more efficiently

  - 0.07 – 7% ID (mice and men)

  - % target accumulation is not a goal in itself

Nanoparticle types: often unfavourable PK



Perspective/Meta-analysis: NP Delivery to Tumours
Wilhelm et al, Nat Rev Mat 1, 16014, 2016

NP (differing in size, shape, charge)

Inorganic (gold, silica, iron oxide, quantum dots, other)

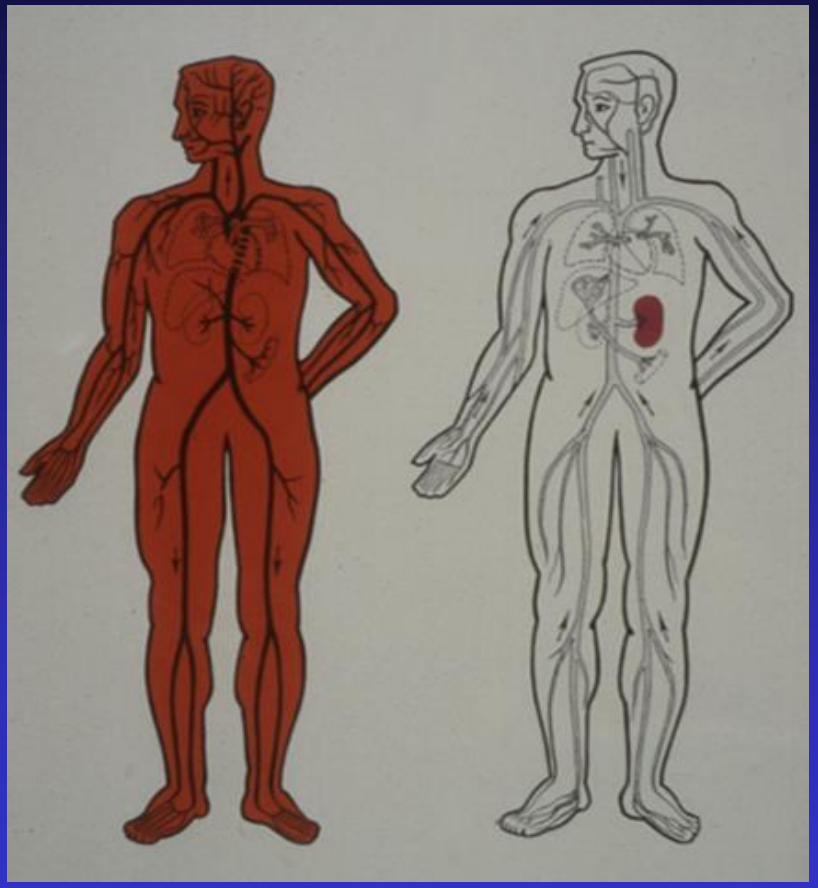
Organic (dendrimers, liposomes, hydrogels, polymeric, other)

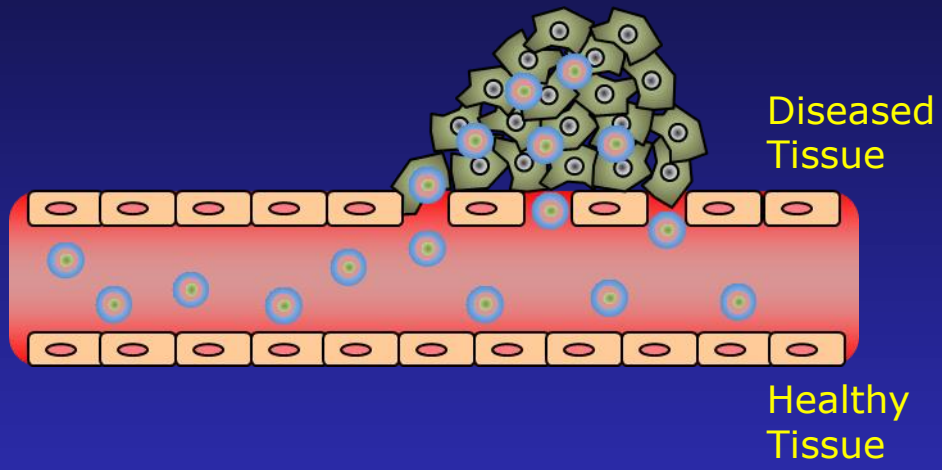
Main outcome (based on 117 manuscripts)

"In preclinical tumor models, on average,

only 0.7% of the injected dose of intravenously administered nanoparticles accumulates in tumours"

Passive Drug Targeting Utilising EPR
Requirements



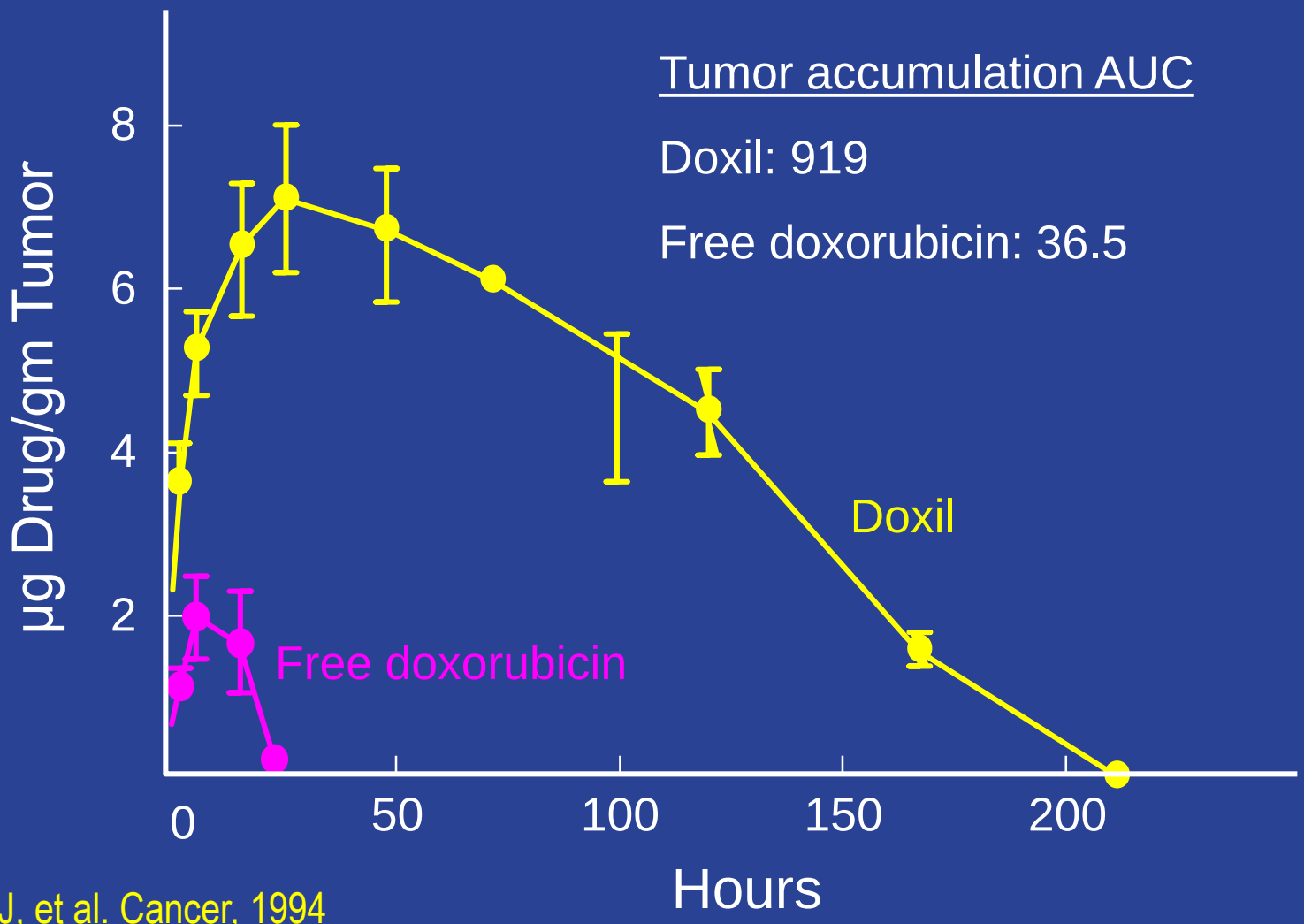


- Passive Targeting requires
  - Nanosize
  - Long circulation
  - No/limited drug release in bloodstream

Variable tumour accumulation of PEG-liposomes in animal models

- Up to 1-10% ID after IV administration

Doxorubicin Levels in Prostate Carcinoma Xenograft



Vaage J, et al. Cancer, 1994

Tumour accumulation of PEG-liposomes in preclinical models

- Up to 1-10% ID after IV administration
- Compared to free drugs: strong improvement

And in the clinic?

Early examples of tumour accumulation (EPR)of PEG-liposomes in patients:

- Vescan (80s)
- Doxil (80/90s)

Vescan Liposomes for Imaging

rigid and small (40-70 nm): long circulation

$^{111}InCl_3$ actively loaded with ionophore

Per 100 mg lipid		mg
L-α-distearoyl/phosphatidylcholine (DSPC)		80.70
Cholesterol		19.30
Nitrilotriacetic Acid (trisodium salt)		0.03
In-$111Cl_3$MBq (μCi)	2.5-37	(250 - 1000 See Table 1)
Ionophore A23187		0.10

Vescan (Vestar Inc, 1984, **400 patients**)

Successful tumor imaging of a wide variety of solid tumors (no quantification) with small, rigid liposomes (40-70nm, Indium-labeled)

Table 1 Vescan clinical findings for 100 mg lipid dose from a carcinoma Phase III trial (Presant et al., 1994)

Carcinoma	Detected	Total	Rate
Breast	3	5	60.0%
Lung	10	15	66.7%
Head & Neck	9	9	100.0%
Other Tumors	5	9	55.6%
Total All Tumors	27	38	71.1%
Primary Sites	10	12	83.3%
Metastases	17	26	65.4%

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Review article

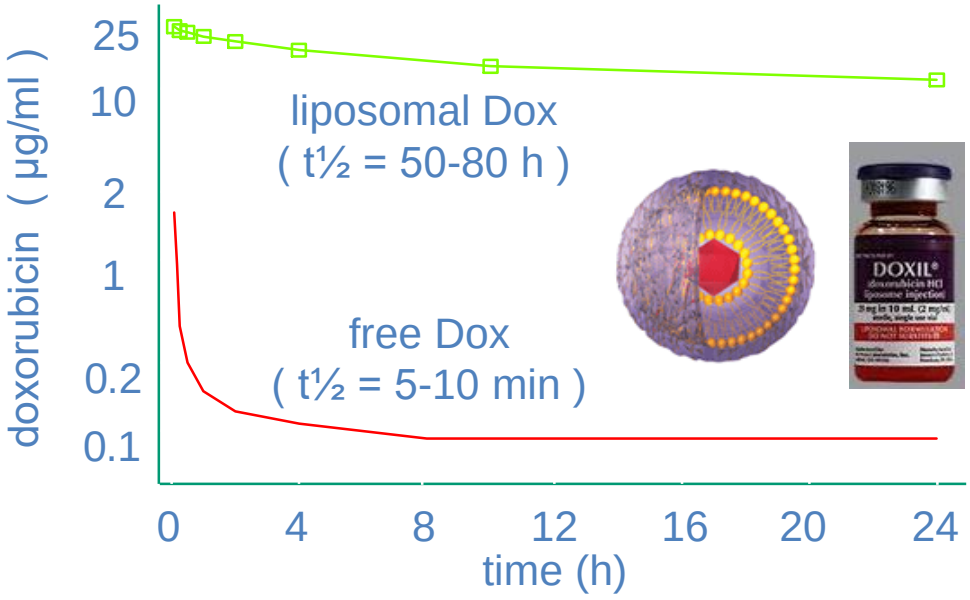
To exploit the tumor microenvironment: Since the EPR effect fails in the clinic, what is the future of nanomedicine?

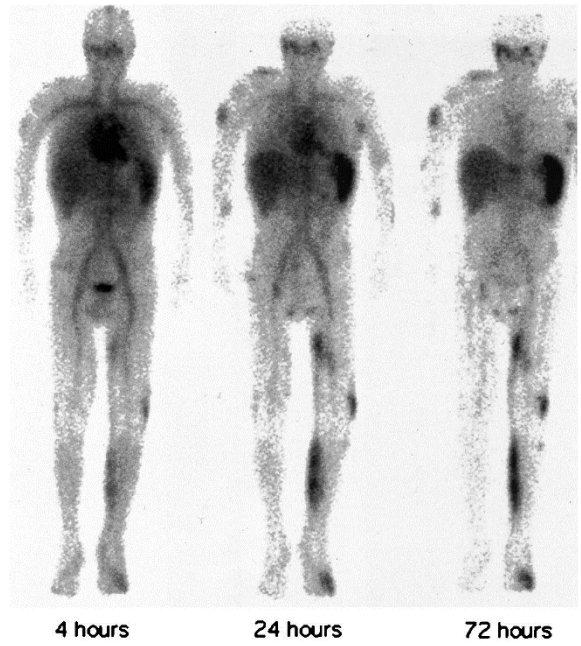
F. Danhier

Université catholique de Louvain, Louvain Drug Research Institute, Advanced Drug Delivery and Biomaterials, Avenue Mounier, 73 bte B1 73.12, 1200 Brussels, Belgium

Reg: KS, ovariumkanker, borstkanker, myeloma

EPR-mediated tumor targeting





in Kaposi sarcoma: <u>improved efficacy</u> vs. ABV => 1 CR + 60/133 PR vs. 31/125 PR

<u>reduced toxicity</u> => less cardiomyopathy, nausea, alopecia (!)

Gabizon et al, Cancer Res (1994)

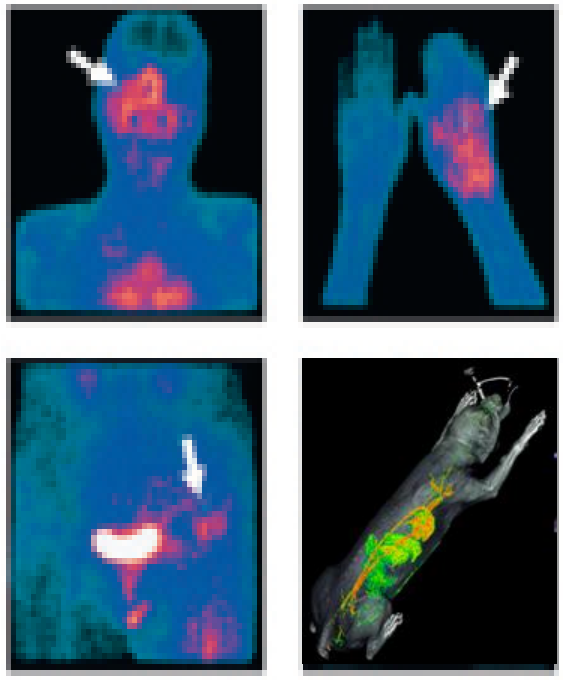
Harrington et al, Clin Cancer Res (2001)

EPR is highly variable

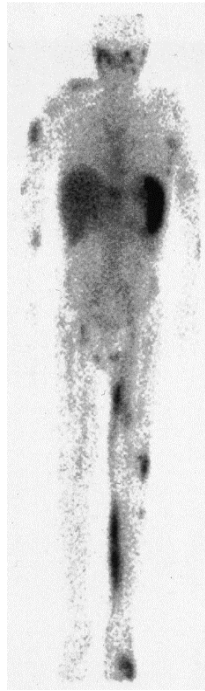
=> in animal models and patients

=> within a single patient and tumor

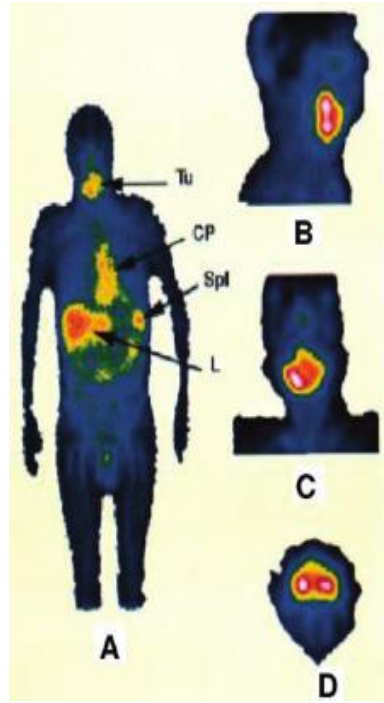
Sarcoma



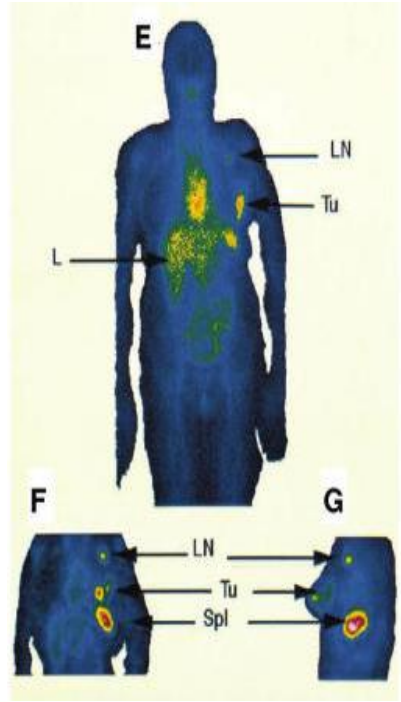
Kaposi S



Head & Neck



Breast

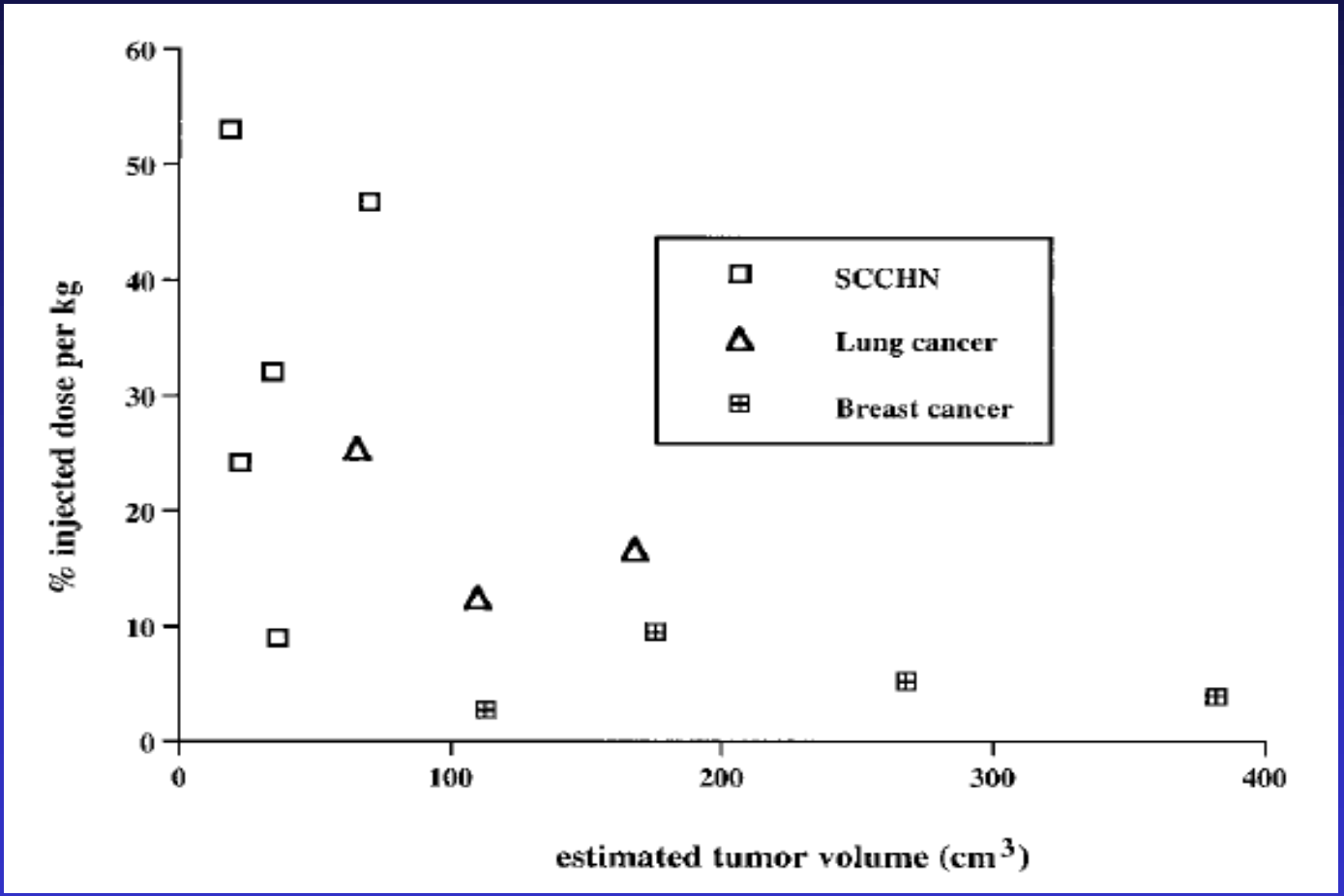


Koukourakis et al, Acta Oncol (2000)

Harrington et al, Clin Cancer Res (2001)

Hansen et al, ACS Nano (2015)

passive drug targeting to tumors via EPR



Not only liposomes..

CRLX101 nanoparticles localize in human tumors and not in adjacent, nonneoplastic tissue after intravenous dosing.

Bioactivity in tumors is demonstrated (down-regulation of topoisomerase I and carbonic anhydrase IX).

Andrew J. Clarka, Devin T. Wileya, Jonathan E. Zuckerman, Paul Webster, Joseph Chao, James Li, Yun Yen, and Mark E. Davis

3850–3854 | **PNAS** | April 5, 2016 | vol. 113 | no. 14

EPR exists
but is highly variable

imaging EPR to pre-select patients
and increase response rate
(personalized nanomedicine)

⇒Companion Diagnostics
(CT/MRI/PET nanoprobes highly needed)

Patient selection step

Key to improve targeted NM performance in the clinic

- Routinely done in case of molecularly targeted therapeutics
- E.g. Herceptin:
  - Biopsy-based preselection
  - Immunohistochemical staining (HER2)
  - Breast cancer patients: response 10-15% without, >50% with preselection

EPR imaging in breast cancer patients

EPR variable; Patient stratification possible; Higher PET/CT signal corresponds with more favorable treatment outcome..

Author Manuscript Published OnlineFirst on March 15, 2017; DOI: 10.1158/1078-0432.CCR-16-3193
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

^{64}Cu-MM-302 Positron Emission Tomography Quantifies Variability of Enhanced Permeability and Retention of Nanoparticles in Relation to Treatment Response in Patients with Metastatic Breast Cancer

Authors: Helen Lee[1*], Anthony F. Shields[2], Barry A. Siegel[3], Kathy Miller[4], Ian Krop[5], Cynthia Ma[3], Patricia M. LoRusso[6], Pamela Munster[7], Karen Campbell[1], Daniel F. Gaddy[1], Shannon C. Leonard[1], Elena Geretti[1†], Stephanie Blocker[2], Dmitri Kirpotin[1], Victor Moyo[1†], Thomas Wickham[1†], Bart S. Hendriks[1]

EPR imaging in pancreas tumor patients

Tumor MRI signal and liposomal drug activity correlate!

Author Manuscript Published OnlineFirst on February 3, 2017; DOI: 10.1158/1078-0432.CCR-16-1990
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

Correlation Between Ferumoxytol Uptake in Tumor Lesions by MRI and Response to Nanoliposomal Irinotecan in Patients With Advanced Solid Tumors: A Pilot Study

Authors

Ramesh K. Ramanathan[1,2*], Ronald L. Korn[1,3*], Natarajan Raghunand[4], Jasgit C. Sachdev[1], Ronald G. Newbold[1,3], Gayle Jameson[1], Gerald J. Fetterly[5^], Joshua Prey[5], Stephan G. Klinz[6], Jaeyeon Kim[6], Jason Cain[6^], Bart S. Hendriks[6], Daryl C. Drummond[6], Eliel Bayever[6^], Jonathan B. Fitzgerald[6]

Patient selection by noninvasive imaging

Key to improve NM performance in the clinic

- *Now*

  Tumor accumulation

- *Soon*

  Tumor vasculature characteristics

  &

  Pharmacological/Physical modulation

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ADR-13146; No of Pages 17

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Pharmacological and physical vessel modulation strategies to improve EPR-mediated drug targeting to tumors

Tarun Ojha [a,b], Vertika Pathak [a], Yang Shi [a], Wim E. Hennink [b], Chrit T.W. Moonen [c], Gert Storm [b,d], Fabian Kiessling [a,*], Twan Lammers [a,b,d,*]

[a] Department of Nanomedicines and Theranostics, Institute for Experimental Molecular Imaging (ExMI), RWTH Aachen University Clinic, 52074 Aachen, Germany
[b] Department of Pharmaceutics, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, 3584 CG, Utrecht, The Netherlands
[c] Imaging division, University Medical Center Utrecht (UMCU), Utrecht, The Netherlands
[d] Department of Targeted Therapeutics, MIRA Institute for Biomedical Technology and Technical Medicine, University of Twente, 7500 AE Enschede, The Netherlands

Perspective/Meta-analysis: NP Delivery to Tumours
Wilhelm et al, Nat Rev Mat 1, 16014, 2016

Main conclusions

1. No significant clinical translation of cancer nanomedicines

Quickly rebutted: >500 clinical trials, with about 25% in Phase III (*Clinicaltrials.gov, search on August 5 2016: nanoparticle OR liposome OR micelle*)

Perspective/Meta-analysis: NP Delivery to Tumours
Wilhelm et al, Nat Rev Mat 1, 16014, 2016

Main conclusions

2. A 30-year strategy needed to overcome this problem

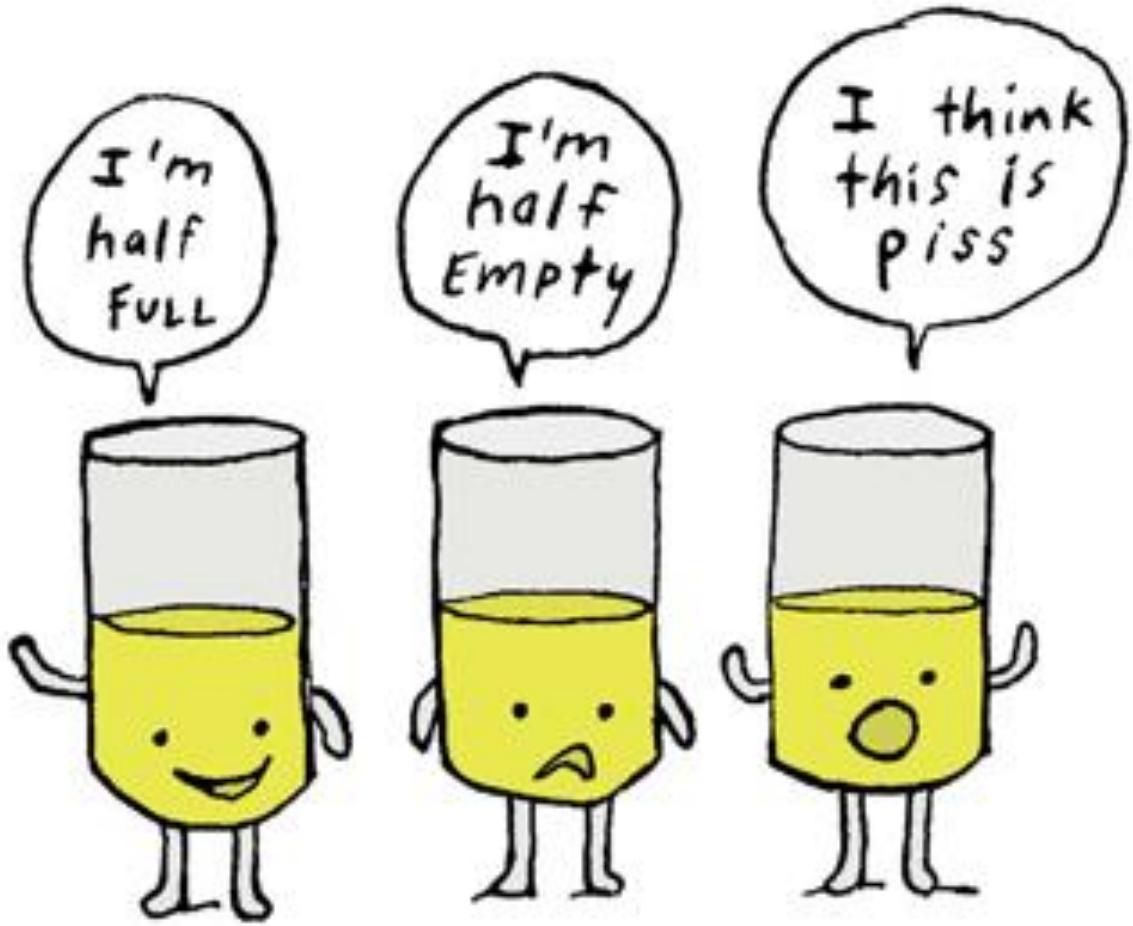
Nanoparticles and Drug Targeting: Future

- To improve clinical translation and patient benefit, **we should not be slow** but stably build on what we know.
- But realise: drug development is costly and has its own slow pace.
- We have made progress and learned a lot.
- Biology is complex: better understanding of in vivo behavior essential
- From formulation-driven to disease-driven development: 'collaborative work attitude' & 'keep it simple' essential

"Friends are readily disappointed by the size of my closet.

And I thought it was big!"

Should we be disappointed?



Pace of clinical translation is indeed slow

Factors: very costly, attitude (big) pharma and investors, complexity (patho)biology underestimated, poor predictive models

We should not be SLOW but stably build on what we know:

- clinical imaging: to assess EPR (companion diagnostics) and tumor vasculature characteristics (density and permeability)
- enhance EPR via pharmacological and physical vessel modulation strategies
- exploit combination treatment regimens (e.g. Vyxeos (liposomal cytarabine/daunorubicin 5/1) and Onivyde (liposomal irinotecan), hyperthermia, radio-, immunotherapy)
- triggered release approaches
- not only cancer but also other diseases
- not only 'old' but also 'new' drugs (incl. biopharmaceuticals)
- targeted delivery of hydrophobic drugs
- animal models with better predictability (e.g. spontaneous and metastatic tumors, also in companion animals, PDX and GEMMs)
- **emphasis should not on novel nanomaterials/nanoparticles, but base strategy on existing (patho)biological understanding and use clinically acceptable systems**

ILLUSTRATION BY **AMY HOJNACKI**