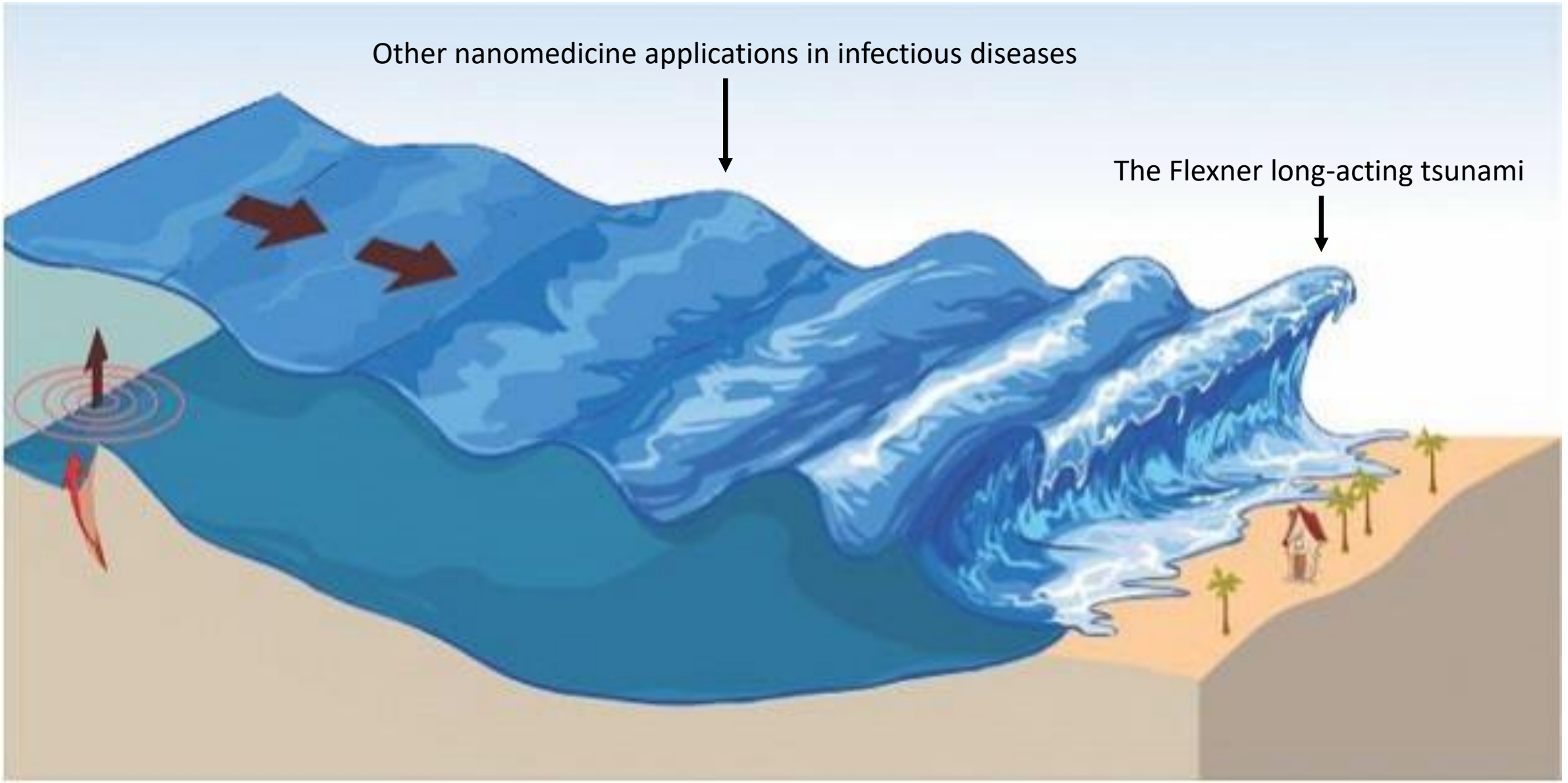
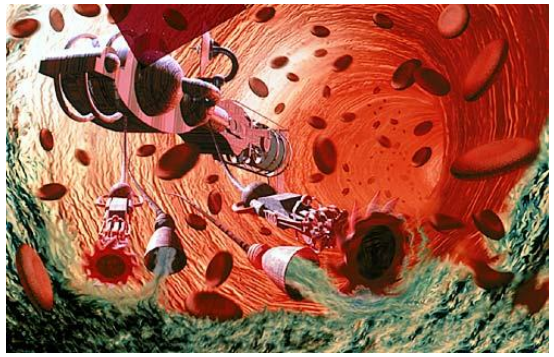
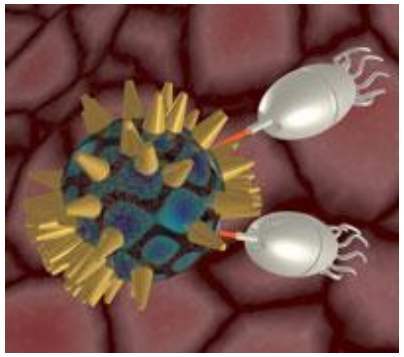
Are you ready for the nanoworld?

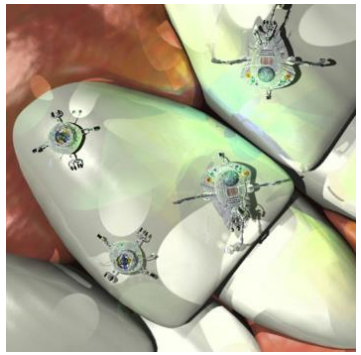
Andrew Owen, Ph.D. FRSB. FBPhS. FLSW.
Professor of Pharmacology, Department of Molecular and Clinical Pharmacology,
University of Liverpool, UK

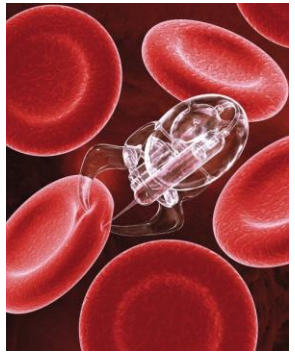

Other nanomedicine applications in infectious diseases
The Flexner long-acting tsunami

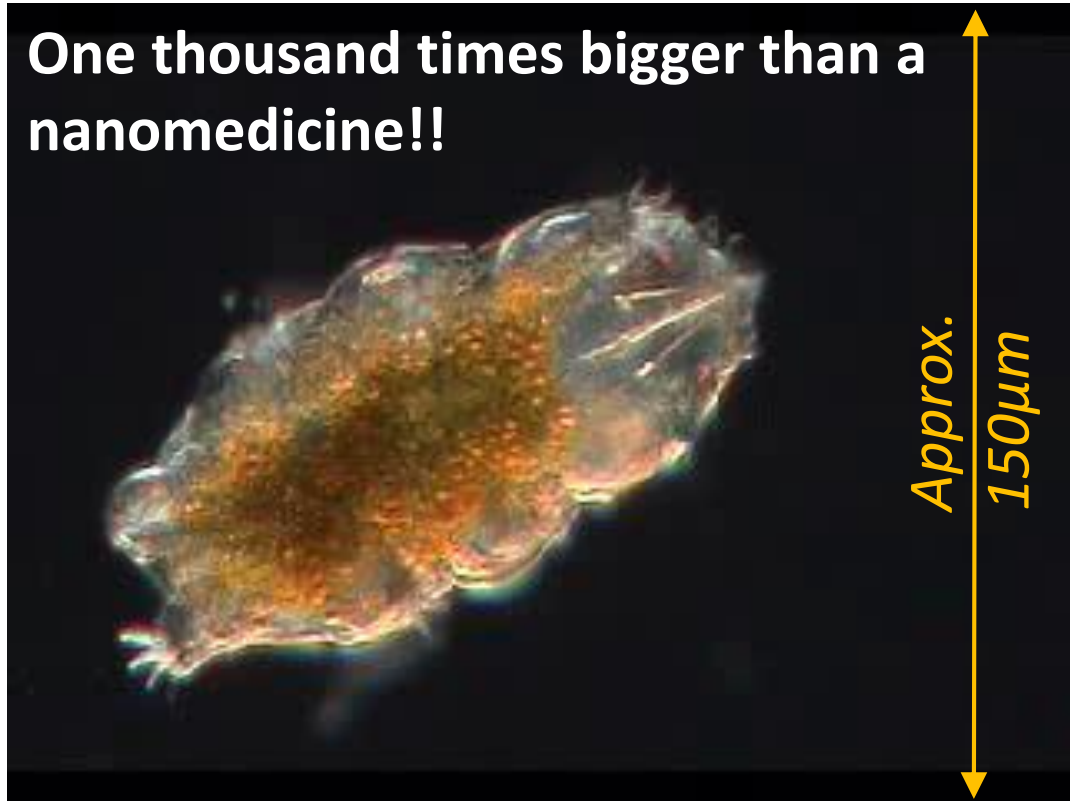
Science fiction versus 3.8 billion years of evolution….











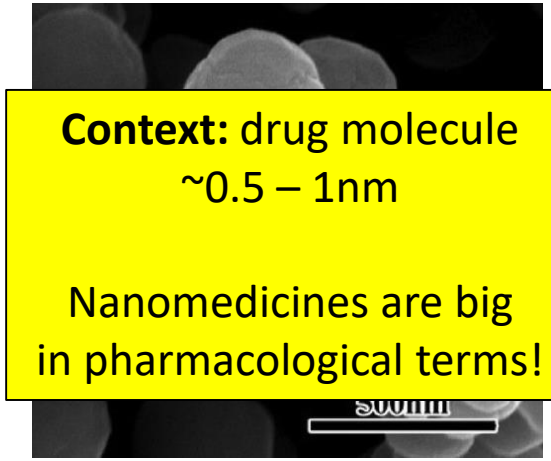
Based on the speed in this video the tardigrade is traveling at ~18 cm / hour

Nanomedicine - size in perspective

Colosseum diameter:
190 metres

Football diameter:
22 centimetres

Espresso grind particle diameter:
250 micrometres



Drug nanoparticles:
300 nanometres

Context: drug molecule ~0.5 – 1nm

Nanomedicines are big in pharmacological terms!

Approximately 863-times smaller

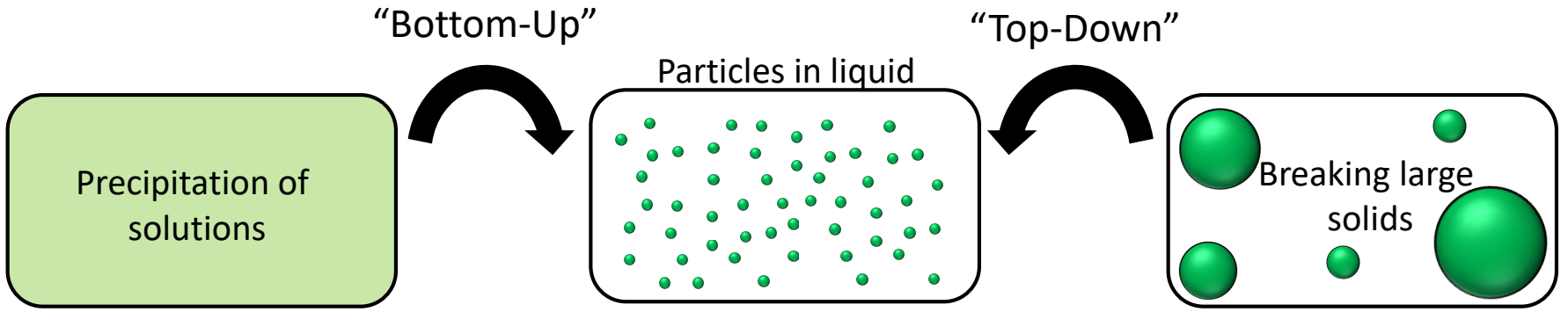
Approximately 863-times smaller

Approximately-863 times smaller

Nanotechnologies being explored in drug delivery

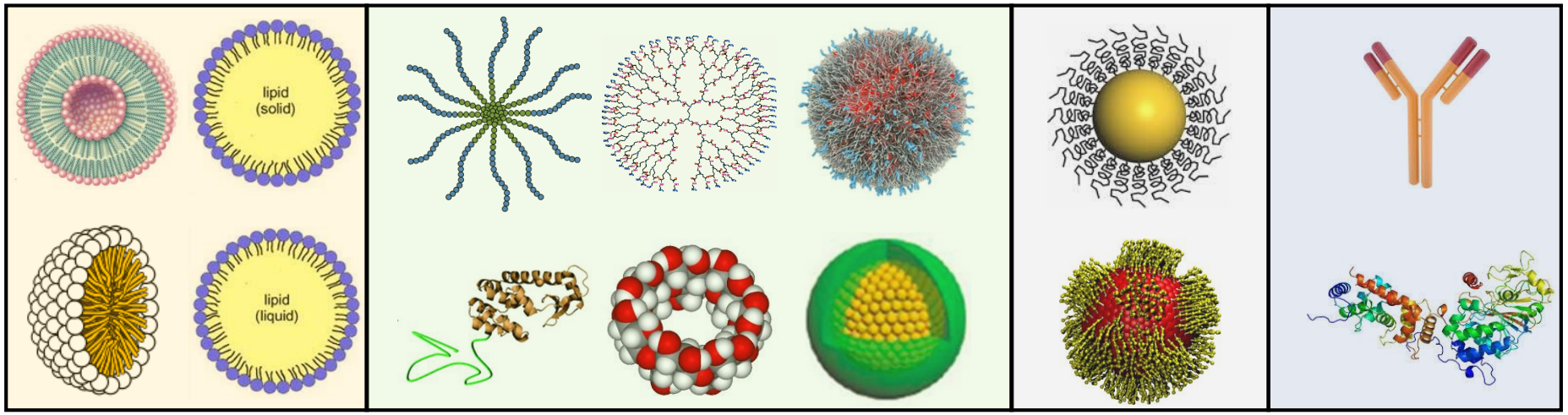
Solid Drug Nanoparticles (Used for improving oral bioavailability and long-acting injectables)

Simple manufacturing process
Regulatory simplicity
Don't have to be expensive



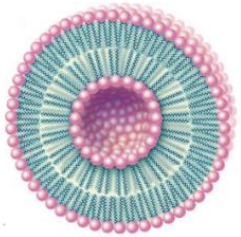
Nanocarrier systems (predominantly relevant to future drug targeting strategies)

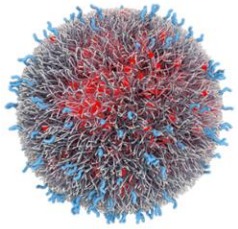
Complex manufacturing
Regulatory complexity
Generally high cost



Lipid-based carriers | polymer-based carriers | Inorganic carriers | Biological

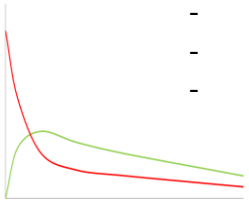
Risk/cost : benefit considerations for nanomedicine development



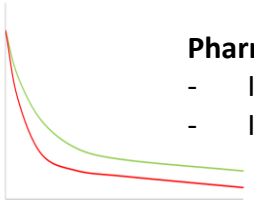


Pharmacological opportunities

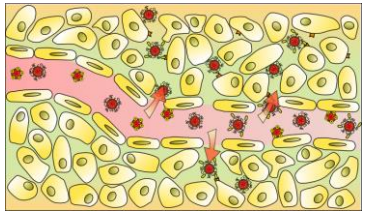
Materials and regulatory complexity



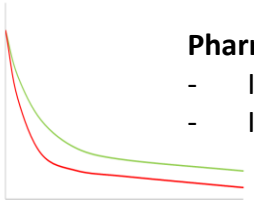
Pharmacokinetic control
- Reduced dose
- Intravenous to oral
- Oral to long-acting



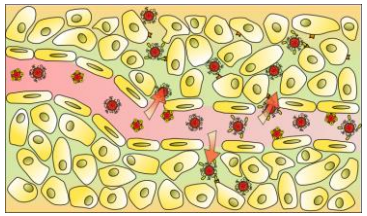
Pharmacokinetic control
- Intravenous
- Increased residence



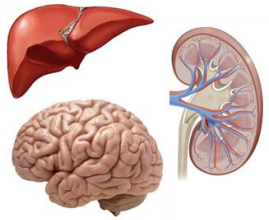
Passive targeting
- EPR effect
- Reduced toxicity



Pharmacokinetic control
- Intravenous
- Increased residence

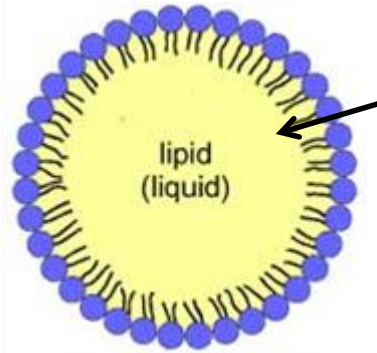


Passive targeting
- EPR effect
- Reduced toxicity

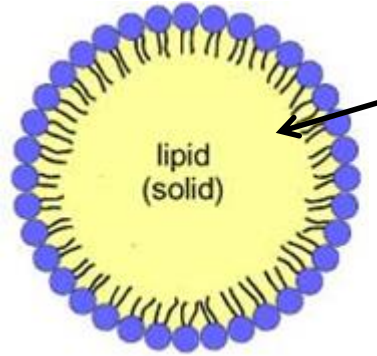


Active tissue/tumour targeting
- Intravenous
- Active targeting (surface ligands, antibodies, aptamers)

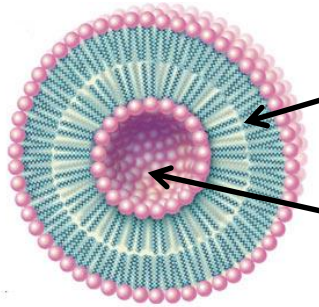
Basic principles of nano-carriers (lipid and polymeric)



Water-insoluble drug dissolved in **lipophilic liquid** lipid core

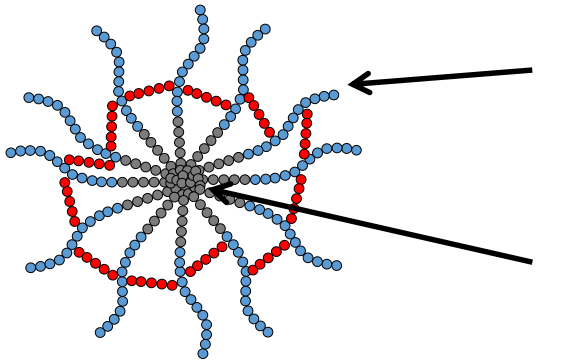


Water-insoluble drug dissolved in **lipophilic solid** lipid core



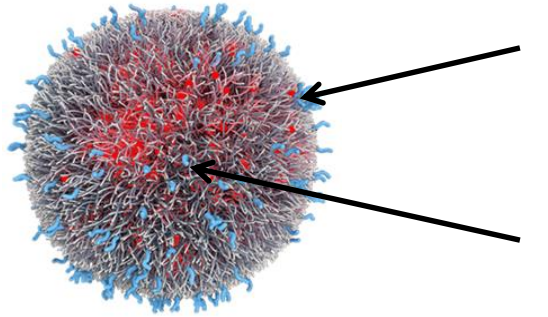
Water-insoluble drug dissolved in **lipophilic lipid bilayer**

Water-soluble drug dissolved in **hydrophilic core**



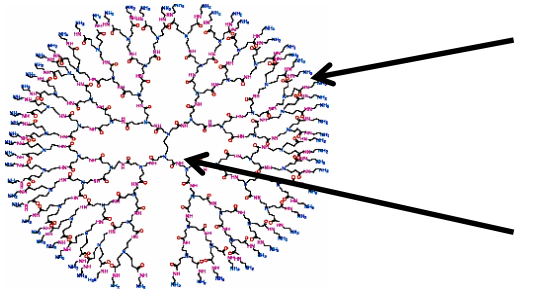
Drug or functional group on surface

Drug in core



Drug or functional group on surface

Drug in polymeric core

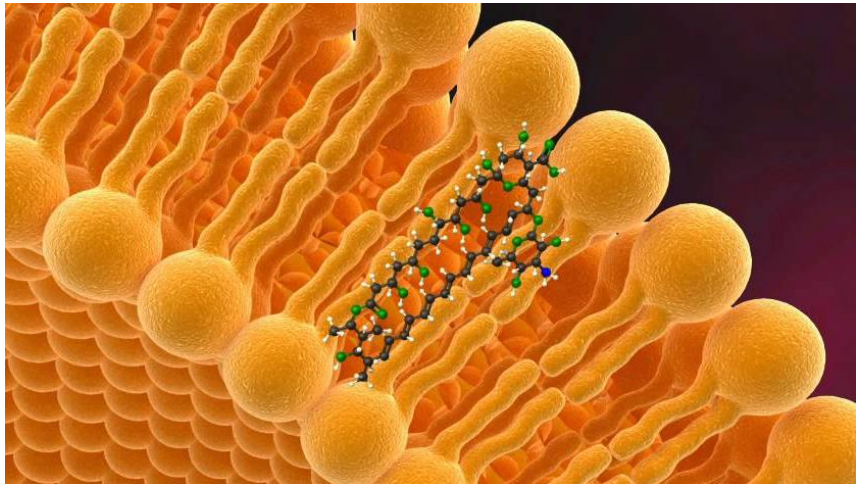


Drug or functional group on surface

Drug in polymeric core

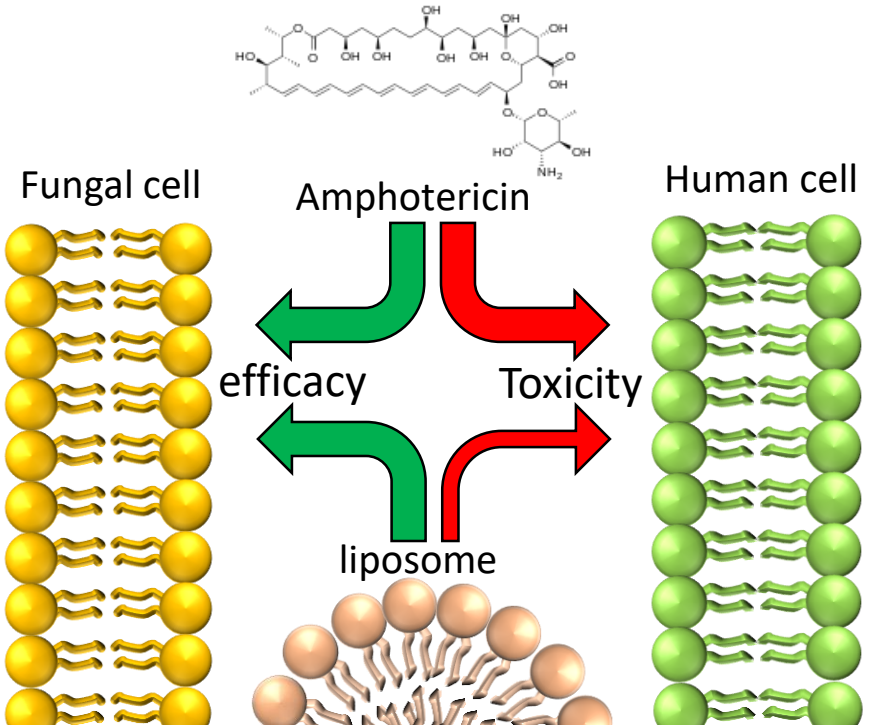
FDA Approved/marketed nanocarrier medicines

Paradigm for passive targeting: Ambisome in the treatment of fungal infections



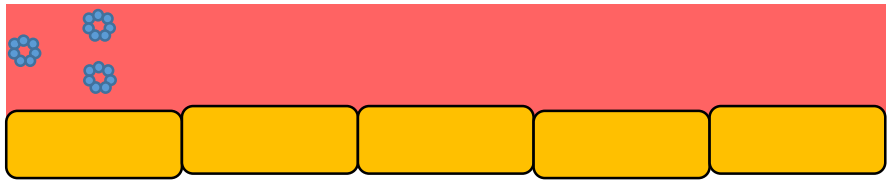
- Ambisome is a liposomal formulation of amphotericin B used to treat serious antifungal infections (e.g. leishmaniasis).
- Clinical studies indicate better safety / tolerability of Ambisome but comparable efficacy to conventional amphotericin.
- Benefit stems from “passive targeting” of the fungal cell membrane bilayer.

- The affinity of amphotericin B for the liposome bilayer is higher than that of the human cell membrane but lower than that of the fungal cell membrane.

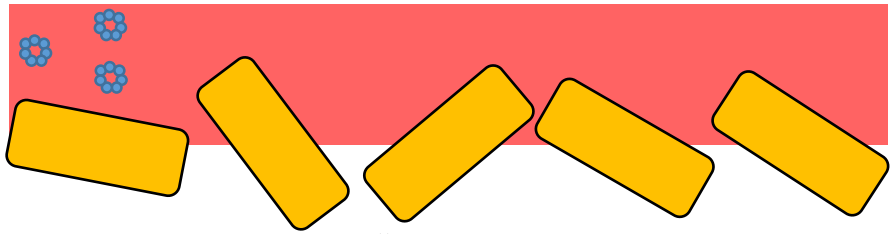


Paradigm for passive targeting: Doxil / Caelyx and the Enhanced Permeation and Retention (EPR) effect

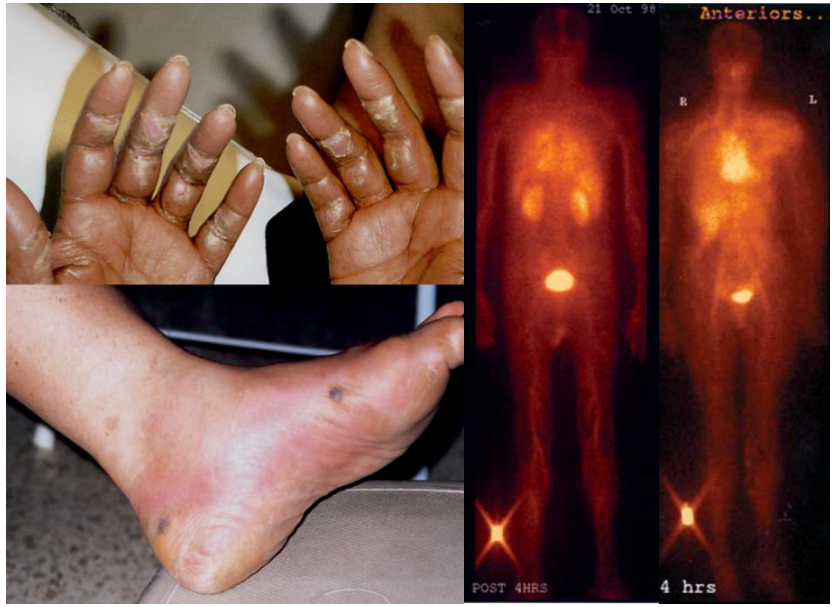
- Doxil is an intravenously administered liposomal preparation of doxirubicin.
- Improvement is dependent upon particles entering the systemic circulation.
- Targeting is based on physiological differences in the tumour. Therefore "passive targeting".



Healthy tissue – normal vasculature

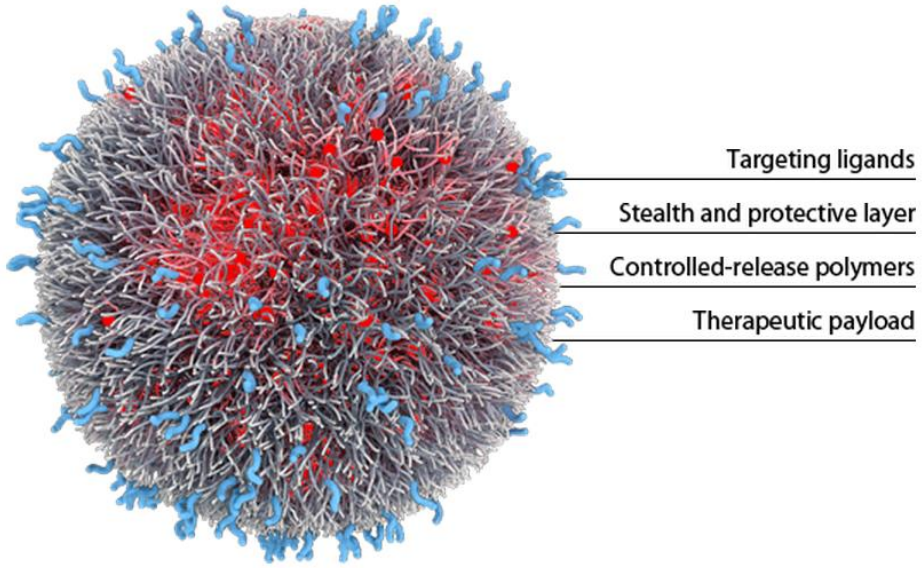


Tumour tissue – "leaky" vasculature



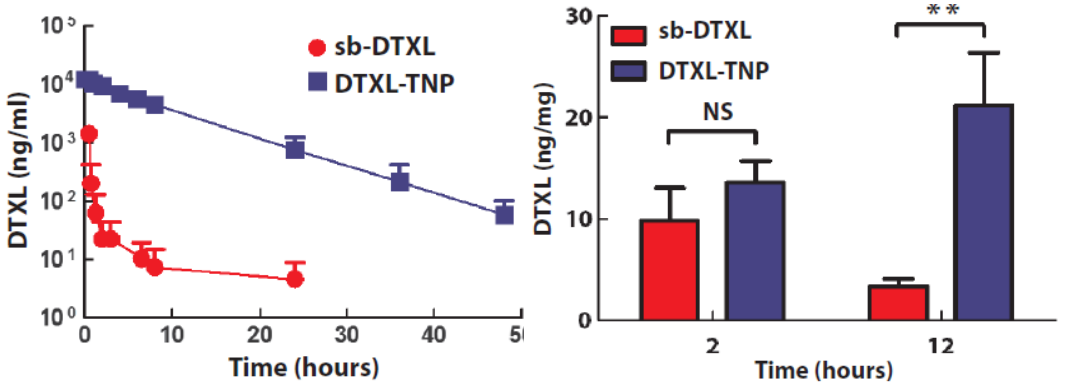
- Doxil is more efficacious than conventional doxorubicin infusion.
- Incidence of cardiotoxicity, alopecia are lower for Doxil.
- However, maximum tolerate daily dose is lower for Doxil because of hand and foot Palmar-Plantar Erythrodysesthesia (PPE).

Paradigms from other diseases: BIND014 and active targeting of cancer cells.



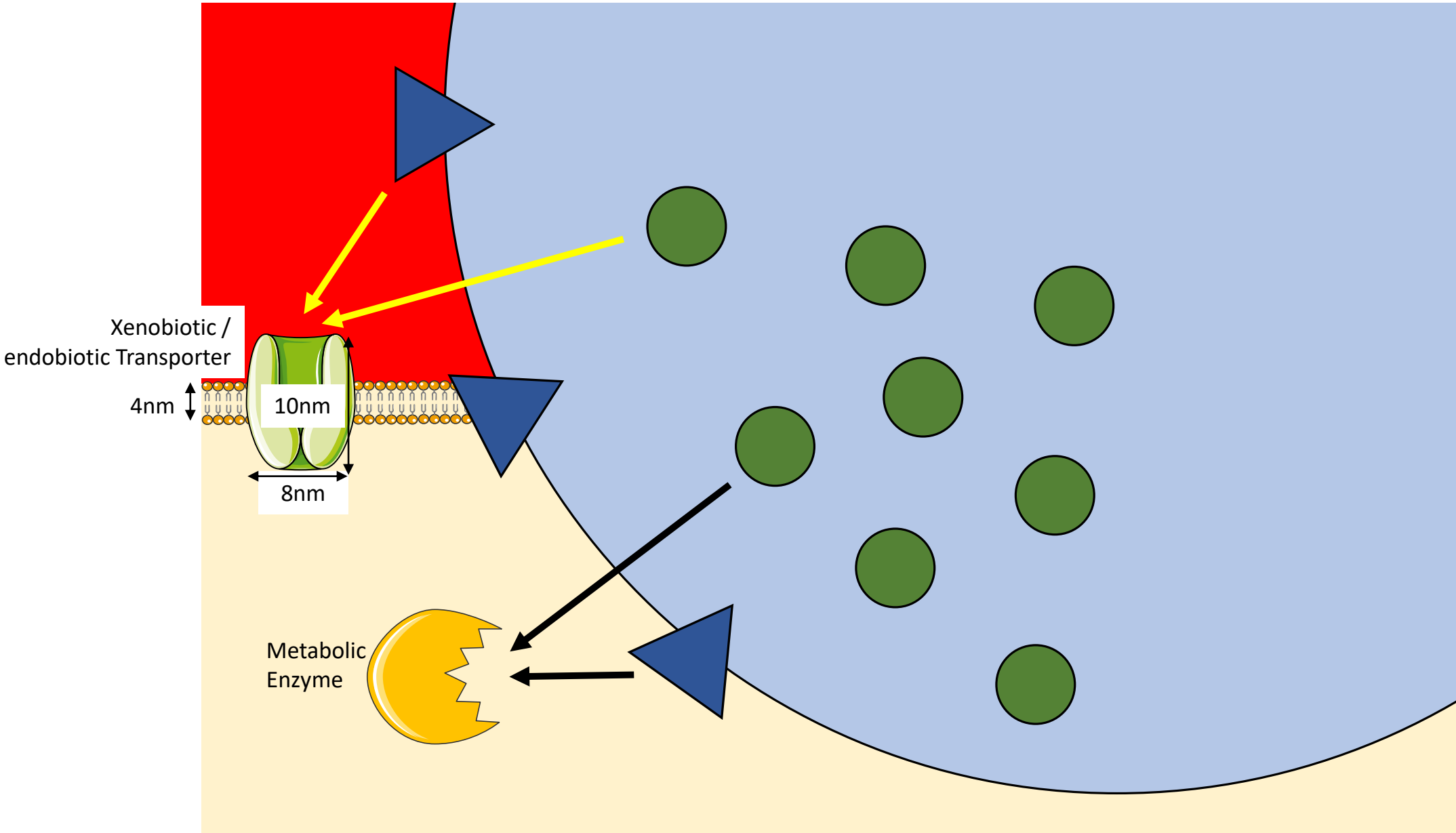
- Circulatory time, EPR effect and recognition of the tumour-specific cell surface protein contribute to higher concentrations within tumour cells.
- Phase II (November 2014) showed superior efficacy over docetaxel with reduced incidence of neutropenia, anaemia, neuropathy and alopecia.

- BIND014 is utilises a targeting ligand directed against *prostate-specific membrane antigen* (PSMA).
- Currently being evaluated with docetaxel but there is flexibility on drug loaded.
- Other companies exploring applications in cancer (e.g. AstraZeneca).



Hrkach et al. Sci Transl Med. 2012 4:128ra39

What do we know about factors influencing nanomedicine disposition?



Additional physicochemical properties of nanoparticles

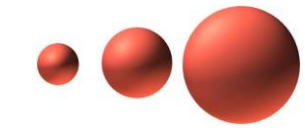
Impact of nanoparticle properties

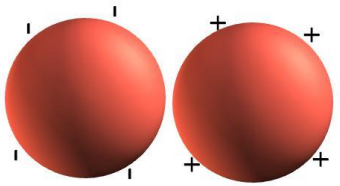
?

Impact of drug properties

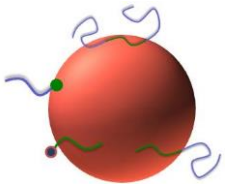
Crystallinity

Particle size
(z-average diameter)

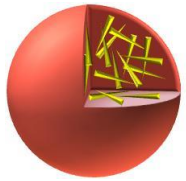


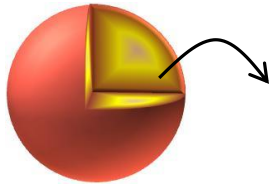


Surface charge
(zeta potential)

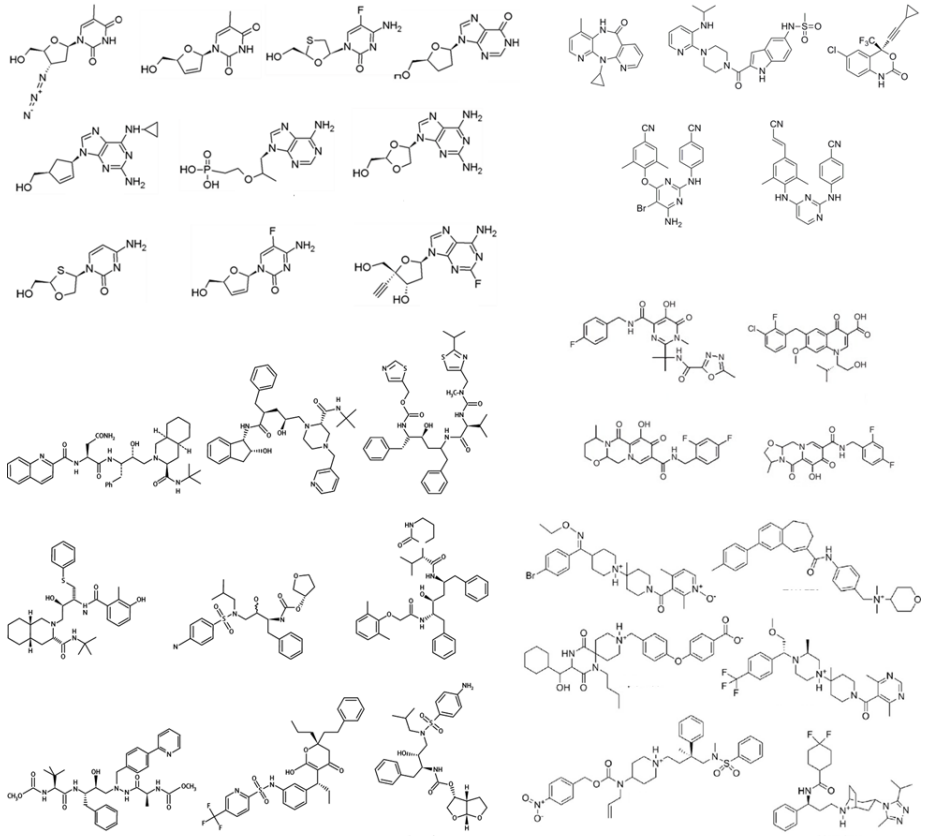


Surface functionality
(e.g. targeting ligands)

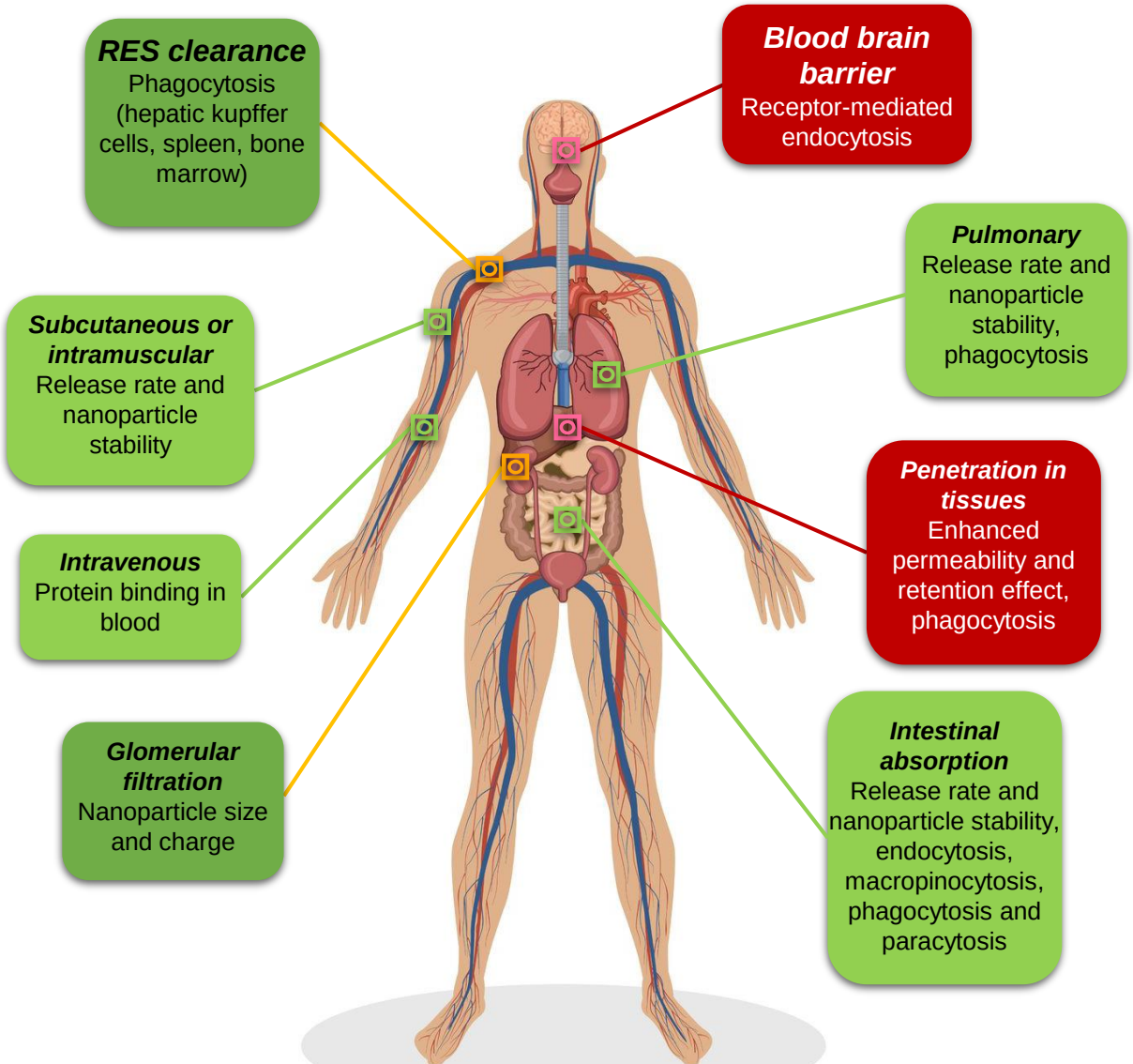


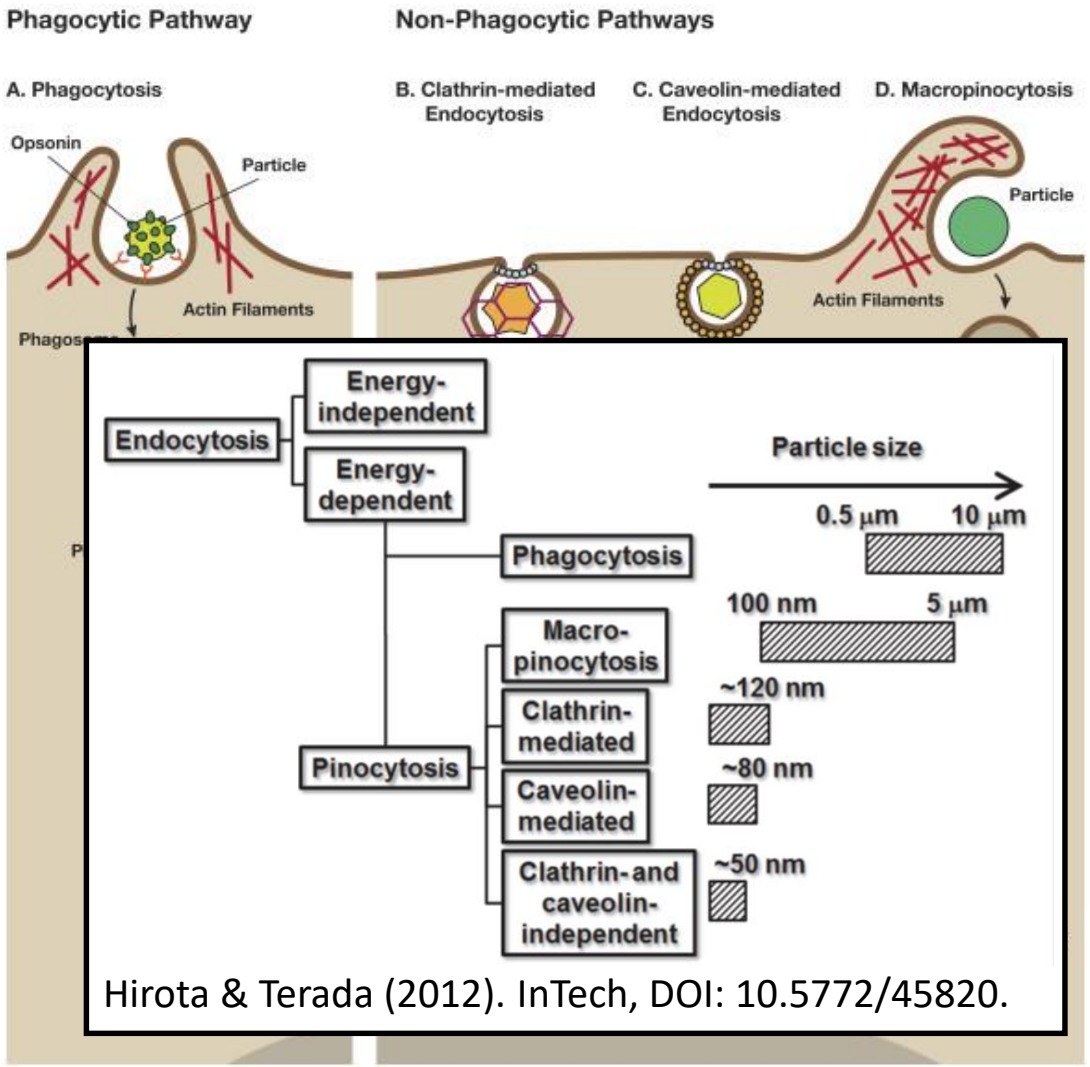


Drug release



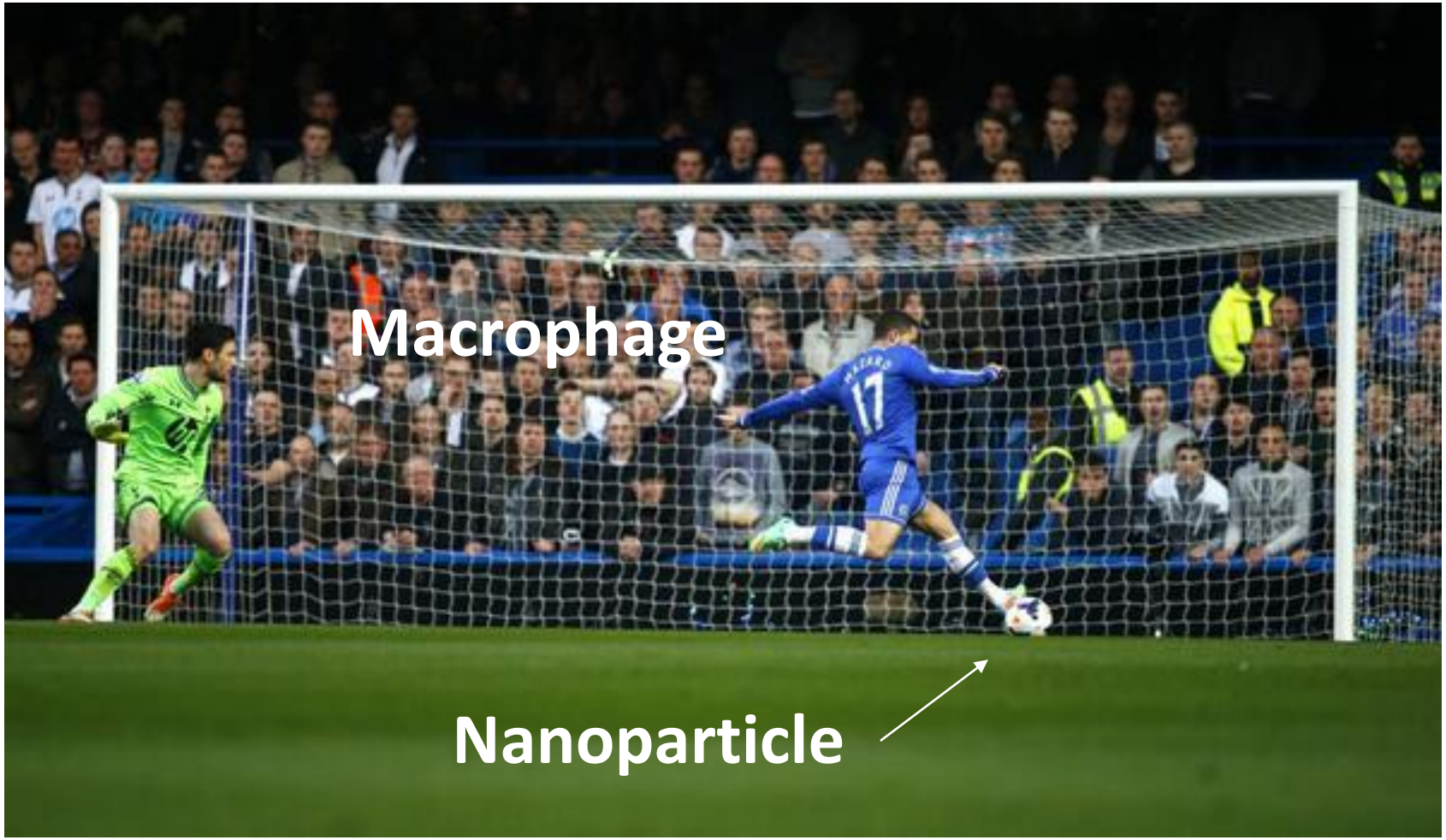
Other mechanisms apply to nanomedicines



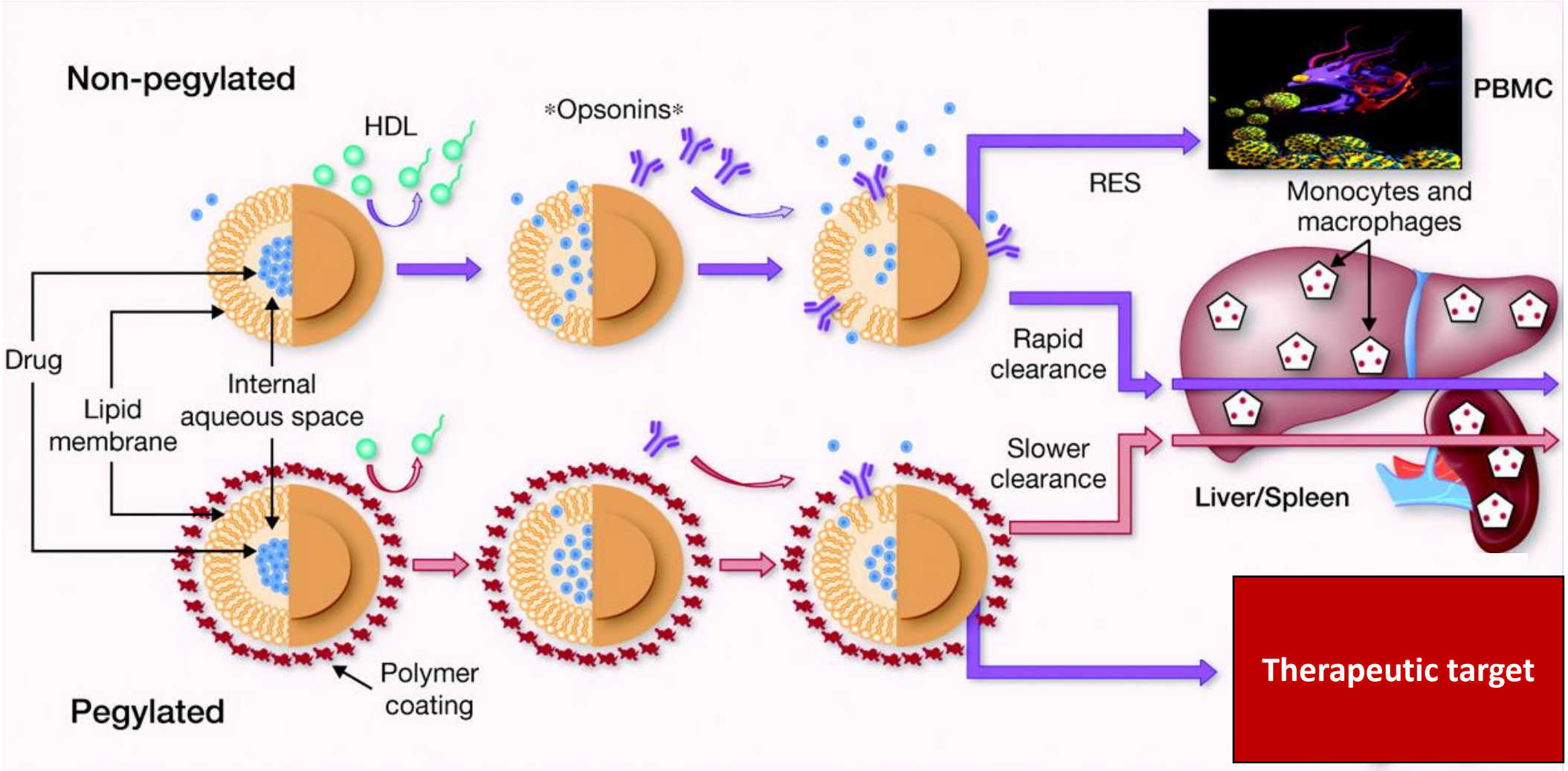


Hirota & Terada (2012). InTech, DOI: 10.5772/45820.

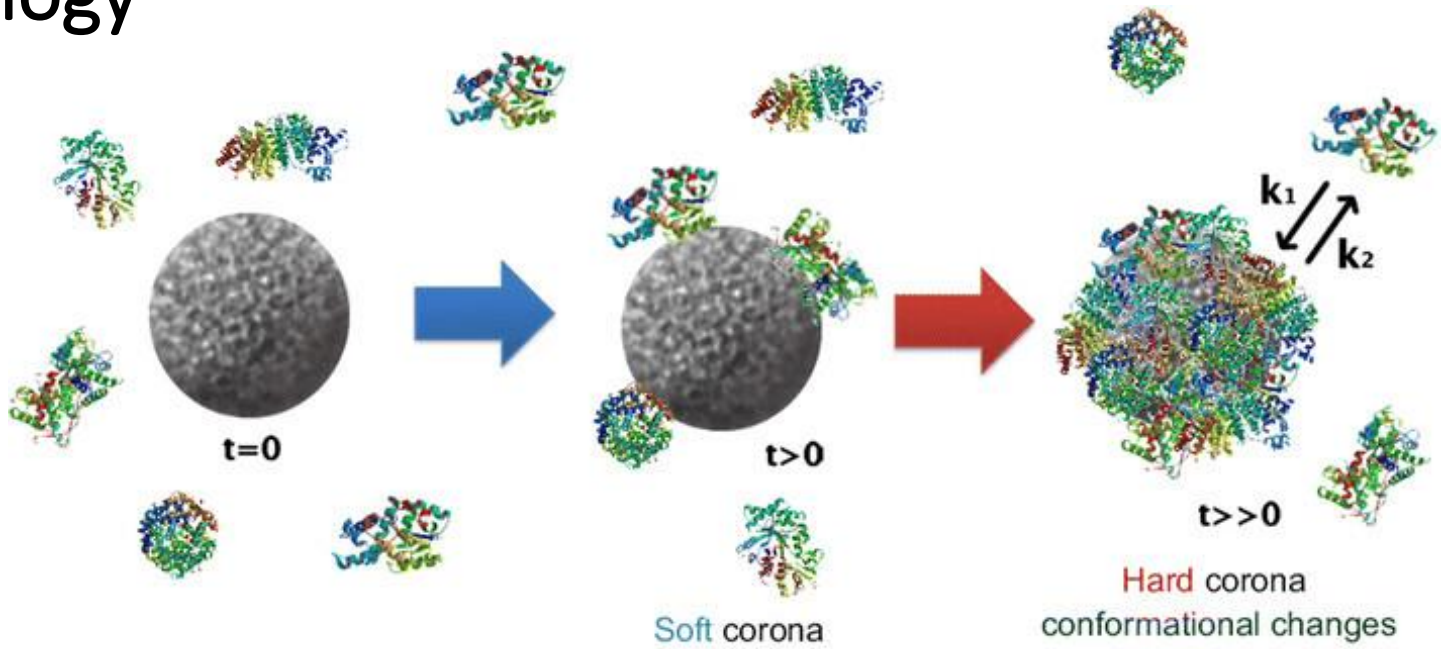
“The macrophage is an open goal for drug delivery with nanoparticles”



Avoidance of the ReticuloEndothelial System (RES) / Mononuclear Phagocytic System (MPS)



The importance of protein corona formation on nanoparticle pharmacology



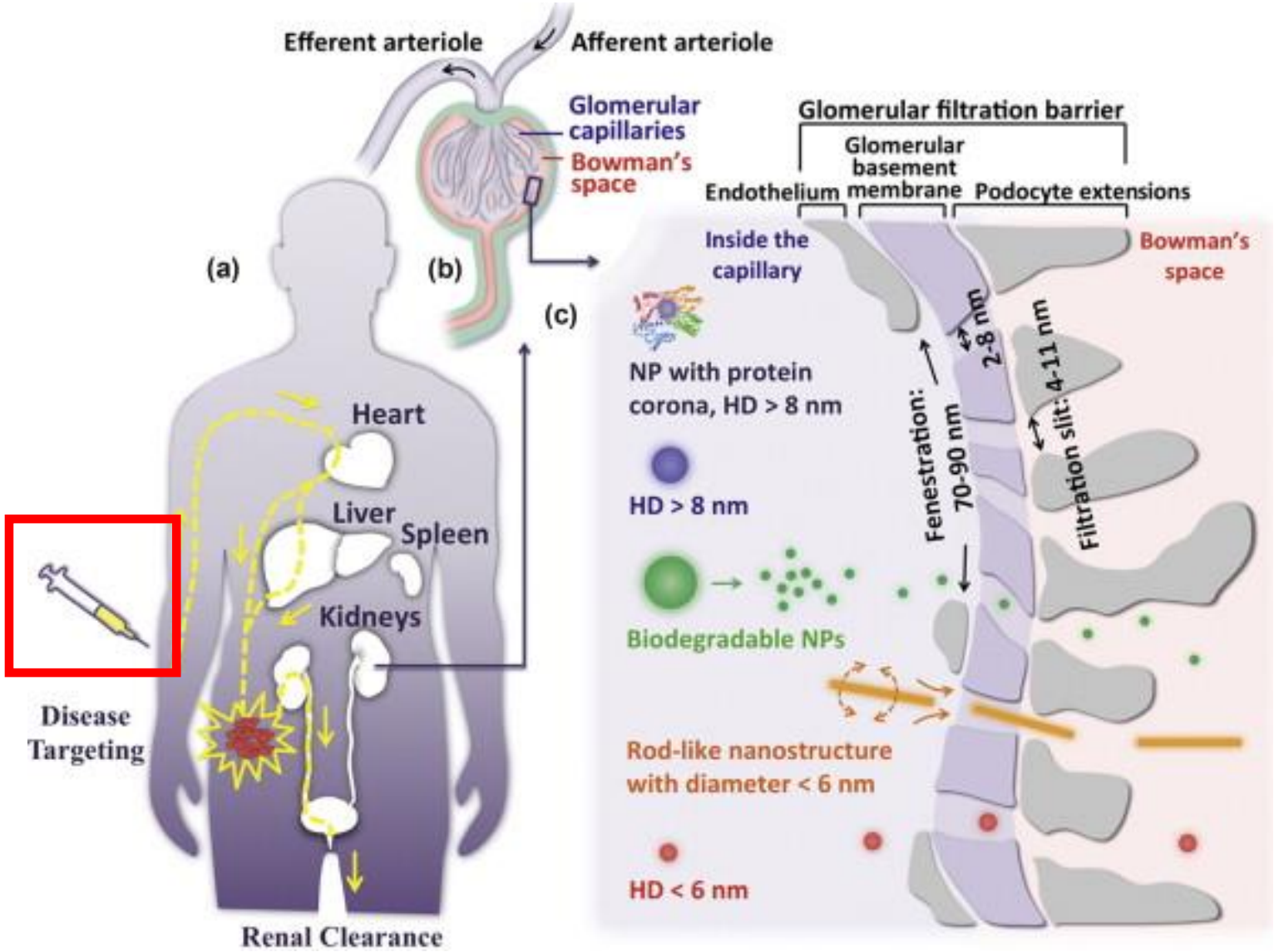
Corona	Soft	Hard
K_d (dissociation constant)[9,20,54]	High	Low
Adhesion to hydrophobicity[35]	Low	High
Molecular weight[25,32]	Low	High
Endosome–Lysosome trafficking[13,21]	Low*	Low*, High†
Conformational changes (sheet)[35,43]	Low	High

Many proteins adhere to the surface of nanoparticles and this is dependent upon the specific biological matrix. For plasma, common proteins include albumin, apolipoproteins, fibrinogen, immunoglobulins and others.

Protein corona formation influences multiple characteristics including:

- Size / surface charge
- Biocompatibility
- Clearance (inc. RES/MPS uptake)
- Immunological interactions (safety)
- Distribution
- EPR effect

Nanoparticle renal clearance (filtration)



Can benefits of nanocarriers within the systemic circulation be achieved from orally dosed materials?

Chemical Science

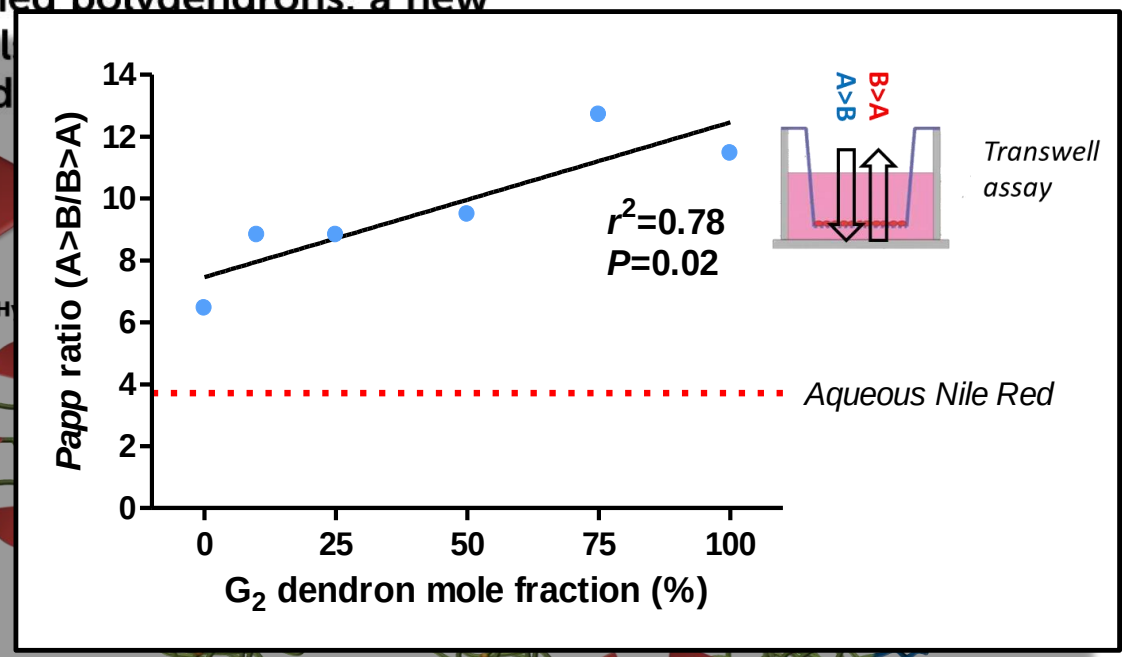
ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2015, **6**, 326

Hyperbranched polydendrons: a new nanomaterial through mod

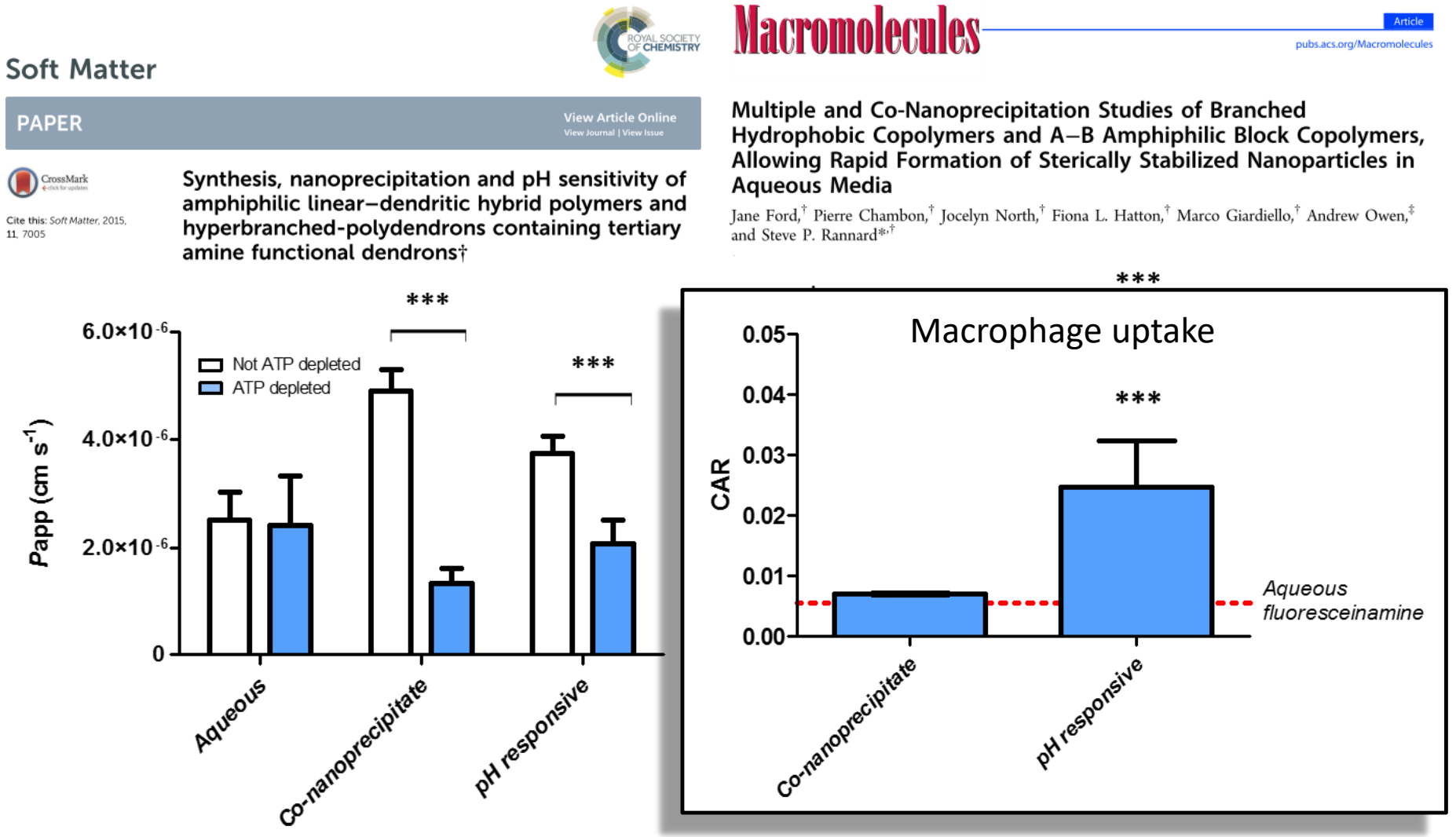


Received 19th September 2014
Accepted 3rd October 2014

DOI: 10.1039/c4sc02889a

www.rsc.org/chemicalscience

Can benefits of nanocarriers within the systemic circulation be achieved from orally dosed materials?



Pharmacology - unpublished

Specific-liver considerations for targeted nanomedicines

Journal of Materials Chemistry B

REVIEW

Diagnostic imaging and therapeutic application of nanoparticles targeting the liver

Haolu Wang,[ab] Camilla A. Thorling,[a] Xiaowen Liang,[a] Kim R. Bridle,[c] Jeffrey E. Grice,[a] Yian Zhu,[cd] Darrell H. G. Crawford,[c] Zhi Ping Xu,*[d] Xin Liu*[a] and Michael S. Roberts*[ae]

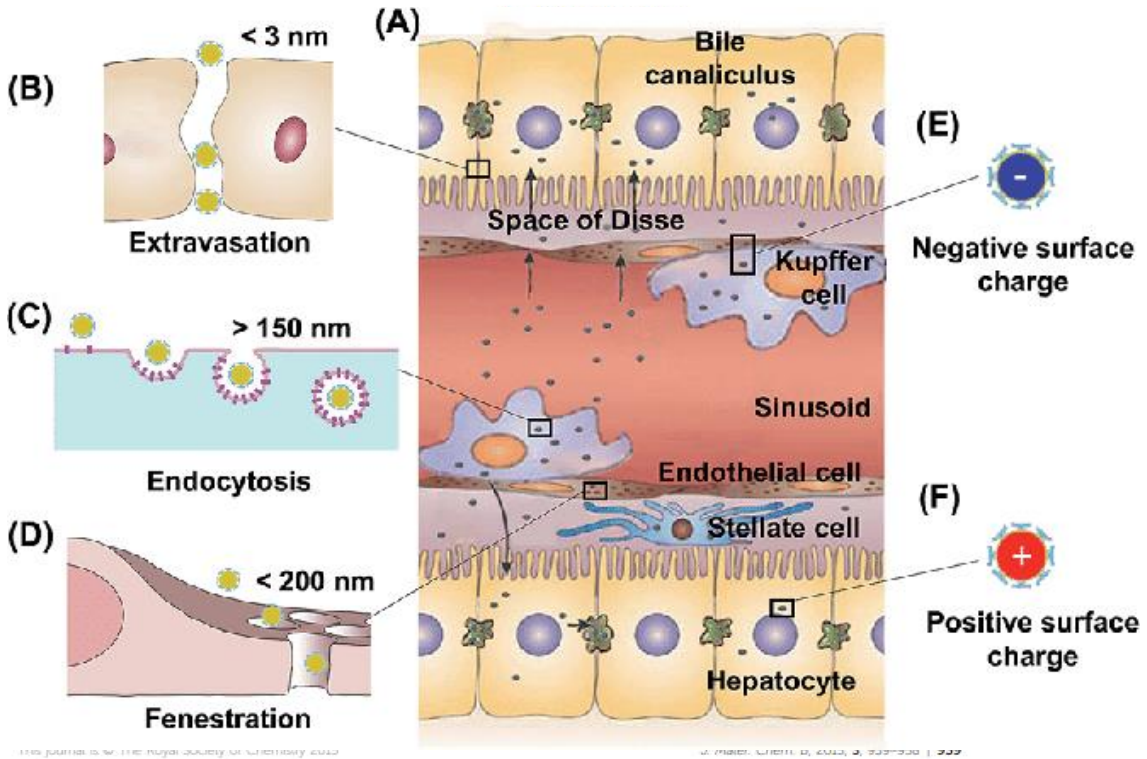
Cite this: J. Mater. Chem. B, 2015, 3, 939

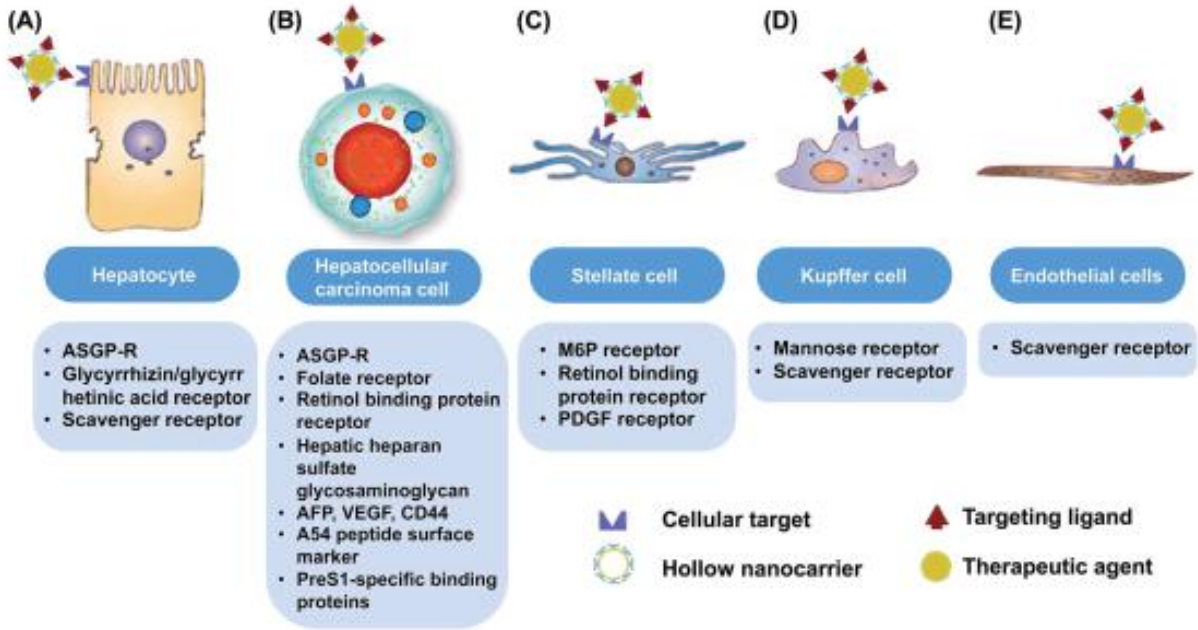
Received 29th September 2014
Accepted 25th November 2014

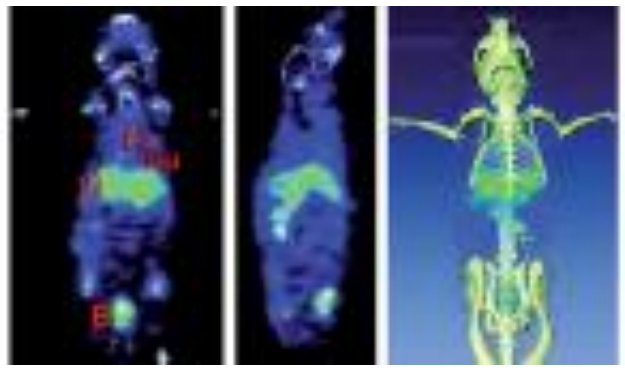
DOI: 10.1039/c4tb01611d

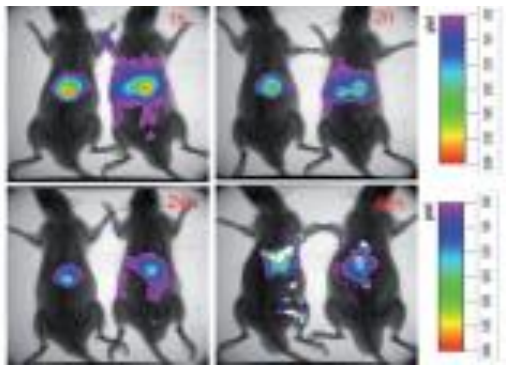
www.rsc.org/MaterialsB

Liver diseases, particularly viral hepatitis, cirrhosis and hepatocellular carcinoma, are common in clinical practice with high morbidity and mortality worldwide. Many substances for diagnostic imaging and therapy of liver diseases may have either severe adverse effects or insufficient effectiveness *in vivo* because of their nonspecific uptake. Therefore, by targeting the delivery of drugs into the liver or specific liver cells, drug efficiency may be largely improved. This review summarizes the up-to-date research progress focusing on nanoparticles targeting the liver for both diagnostic and therapeutic purposes. Targeting strategies, mechanisms of enhanced effects, and clinical applications of nanoparticles are discussed specifically. We believe that new targeting nanotechnology such as nanoprobes for multi-modality imaging and multifunctional nanoparticles would facilitate significant advancements in this active research area in the near future.









Summary and outlook

- The major focus for nanocarrier drug delivery systems has been in oncology but they offer bespoke opportunities for improved passive or active targeting to infected regions of the body.
- Knowledge regarding the pharmacokinetics and distribution of nanoparticles is still evolving but the mechanisms are substantially different than for classical small molecule drugs.
- Understanding the key molecular, anatomical and physiological biology is key to robust assessment of the infection-specific opportunities.
- Existing nanocarrier products involve short-term intravenous delivery, and if they are to be successful in medium- to long-term infections then other routes of delivery need to be explored and exploited.

Acknowledgements

The Liverpool Team

Marco Siccardi
Steve Rannard
Saye Khoo
Neill Liptrott
Marco Giardiello
David Back
Lee Tatham
Paul Curley
Helen Box
Qurat Shabir
Laura Dickinson
Megan Neary
Darren Moss
Alison Savage
Tom McDonald
Chris David
Pierre Chambon
Fiona Hatton
Sam Auty
Andy Dwyer
Hannah Rogers
Faye Hern
Jane Ford

Deirdre Egan
Laura Else
Sara Gibbons
Helen Reynolds
Alessandro Schipani
Rajith Kumar Reddy
Christina Chan
Justin Chiong
James Hobson
Maude LeHellaye
Henry Pertinez
Rebecca Slater
Steph Edwards
Rana Abutaima
Rohan Gurjar
Sharon Murphy
Ana Jimenez-Valverde
Hannah Kinvig
Martin Levere
Louise Tidbury
Adam Town
Helen Cauldbeck
Rana Abutaima

SSAT
Marta Boffito
Akil Jackson
Emilie Elliot

CHAI
Paul Domanico
Melynda Watkins

MPP
Yao Cheng
Sandeep Juneja

JHU
Charlie Flexner
Caren Meyers
Theresa Shapiro
Rahul Bashki

UNMC
Sue Swindells
Kim Scarsi
Courtney Fletcher

Torino
Giovanni DI Perri
Stefano Bonora
Antonio D'Avolio

WITS
Francois Venter
Michelle Moorhouse
Celicia Serenata

Alder Hey
Brian Flannagan
Paul McNamara