Novel Nanotechnologies for antiretroviral drug delivery

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UNIVERSITY OF LIVERPOOL

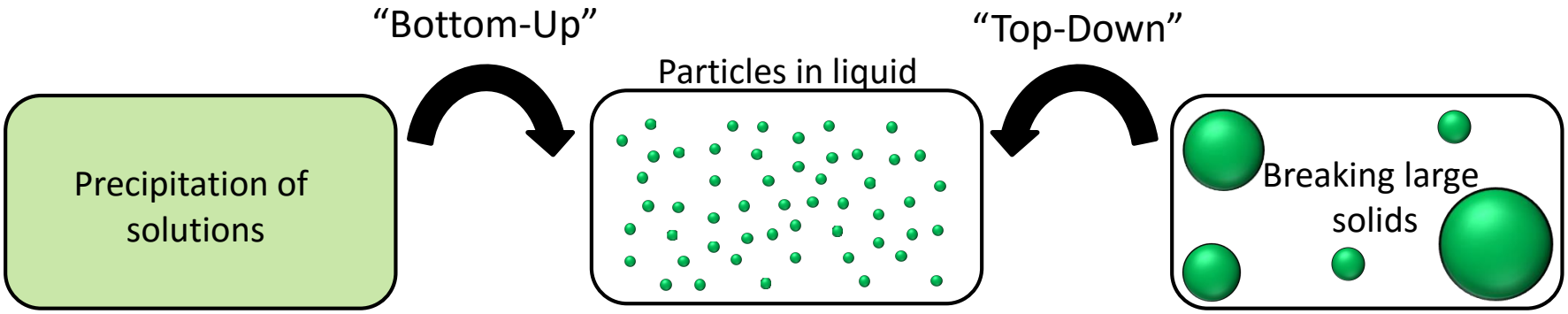
BRITISH SOCIETY FOR NANOMEDICINE

Overview

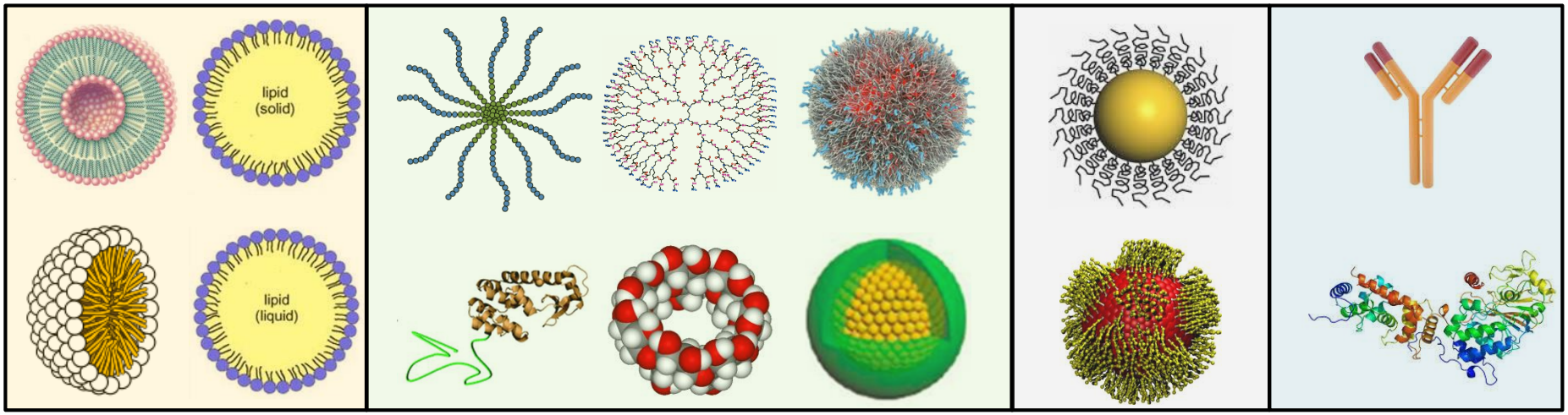
- Introduction
- Nanomedicines for parenteral delivery
  - long-acting drug delivery
  - Nanocarrier approaches for targeted delivery
- Nanomedicines for oral delivery
  - University of Liverpool antiretroviral nanomedicines
- Summary

Nanotechnologies being explored in drug delivery

Solid Drug Nanoparticles (SDNs; aka nanocrystals, nanosuspensions, nanodispersions)

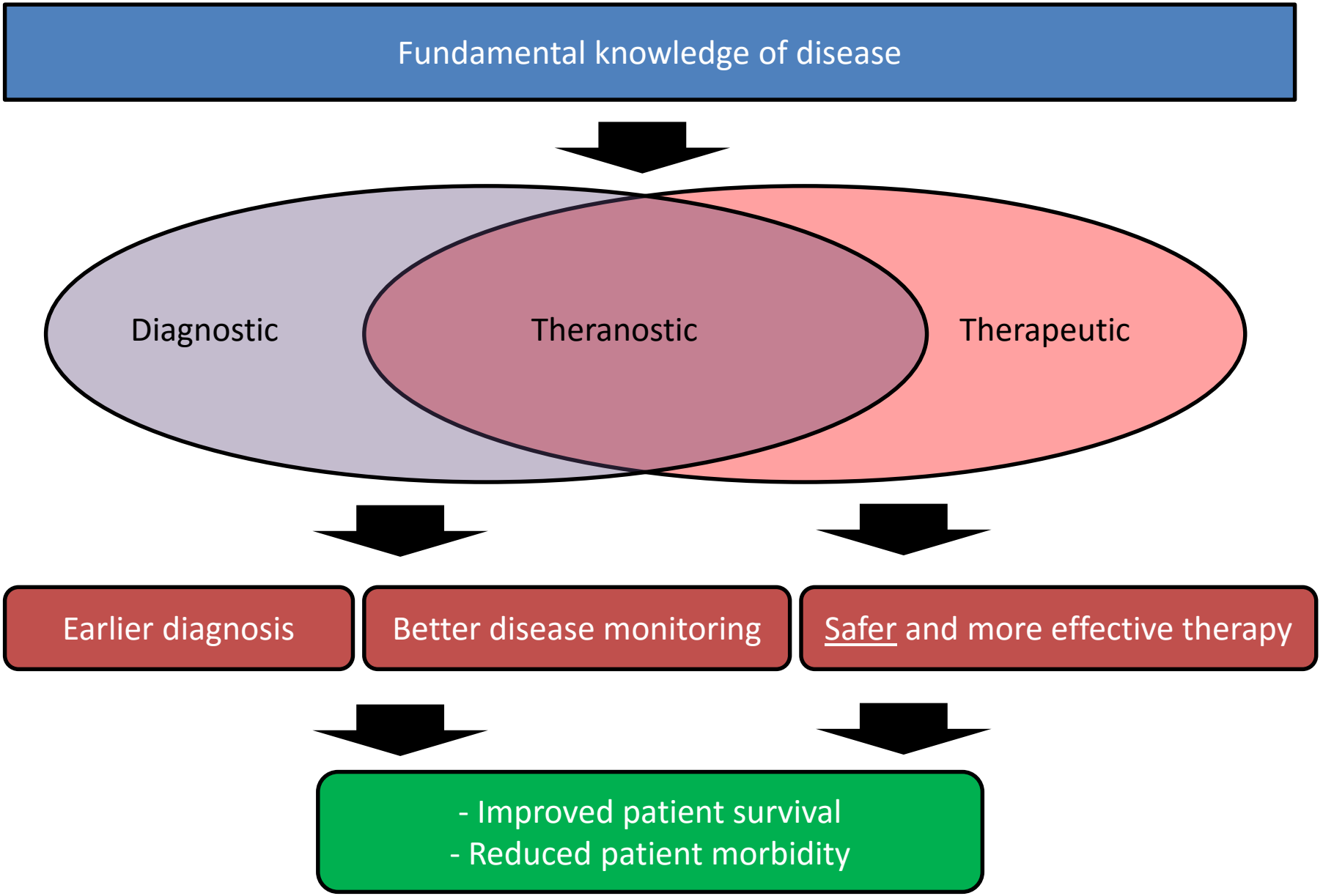


Nanocarrier systems (extremely diverse in composition)



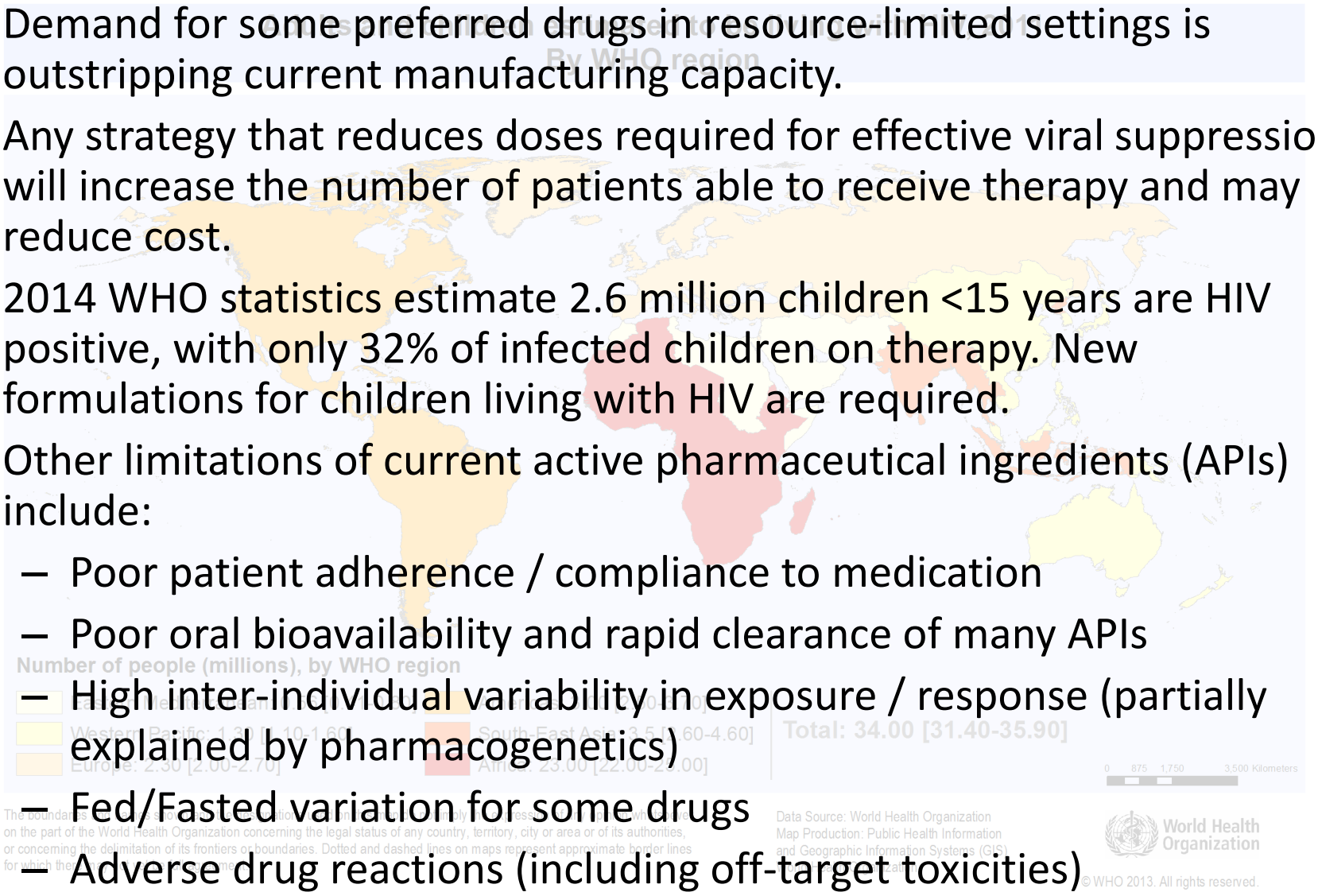
Lipid-based carriers | polymer-based carriers | Inorganic carriers | Biological

Current applications of nanotechnology in medicine

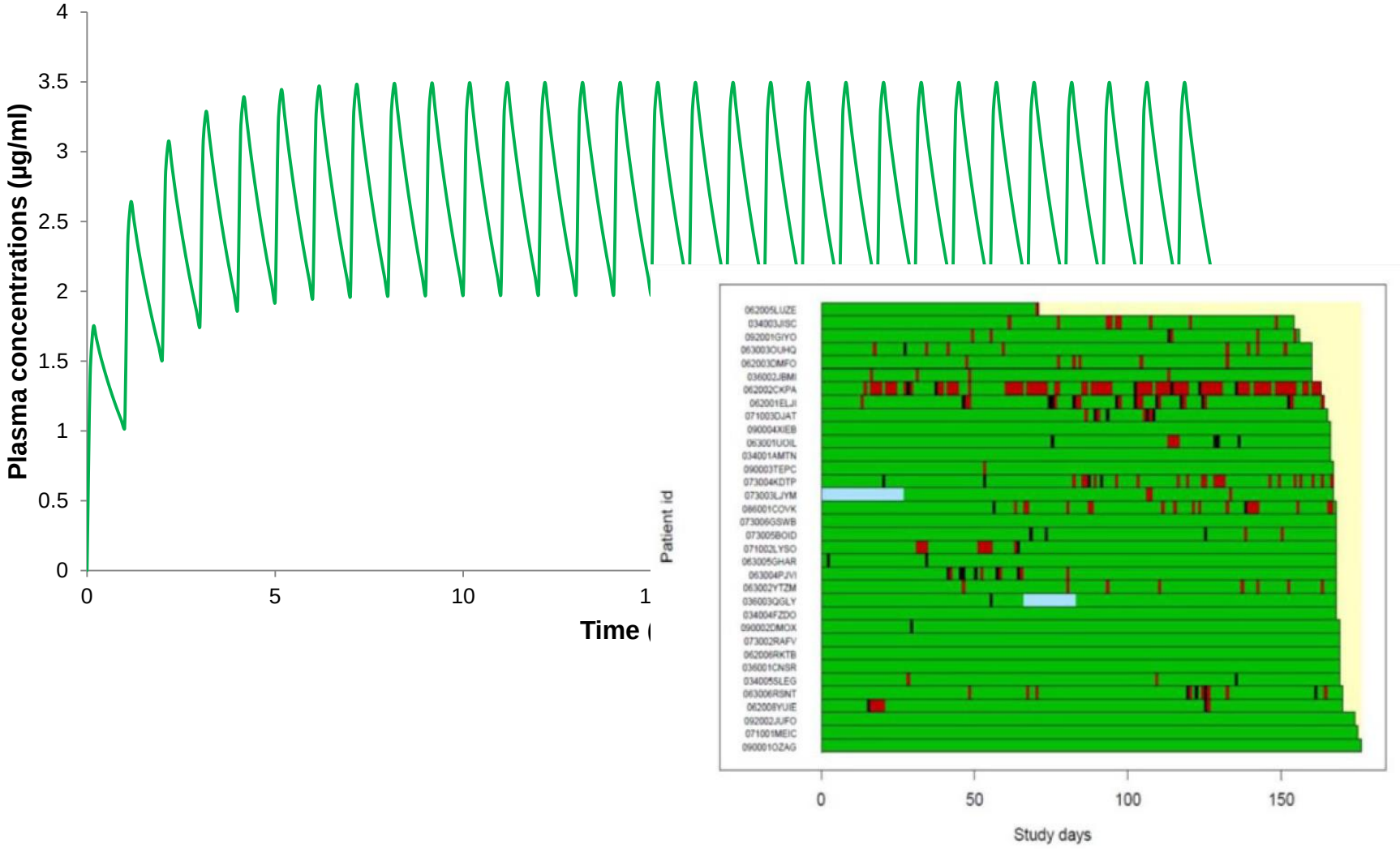


HIV therapy: paediatric considerations

- Demand for some preferred drugs in resource-limited settings is outstripping current manufacturing capacity.
- Any strategy that reduces doses required for effective viral suppression will increase the number of patients able to receive therapy and may reduce cost.
- 2014 WHO statistics estimate 2.6 million children <15 years are HIV positive, with only 32% of infected children on therapy. New formulations for children living with HIV are required.
- Other limitations of current active pharmaceutical ingredients (APIs) include:
  - Poor patient adherence / compliance to medication
  - Poor oral bioavailability and rapid clearance of many APIs
  - High inter-individual variability in exposure / response (partially explained by pharmacogenetics)
  - Fed/Fasted variation for some drugs
  - Adverse drug reactions (including off-target toxicities)

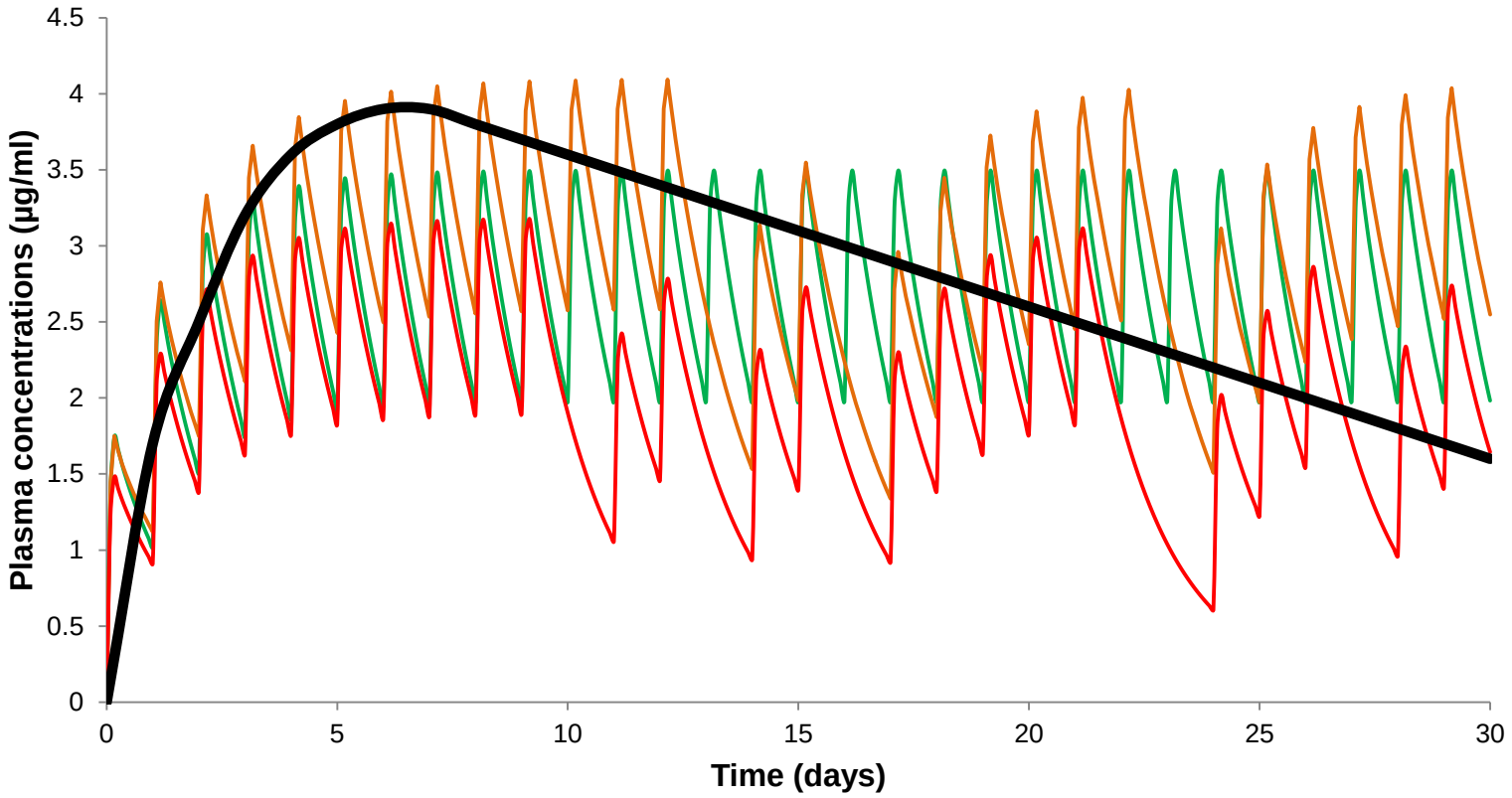


Non-adherence to HIV medication is a key driver for long-acting antiretroviral regimens



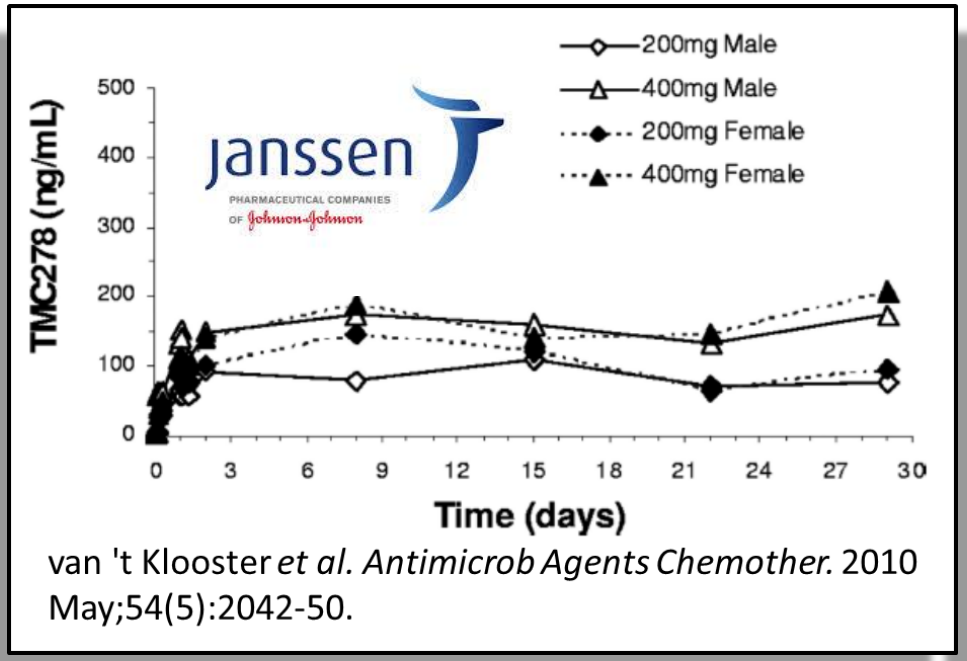
Savic et al 2012

Non-adherence to HIV medication is a key driver for long-acting antiretroviral regimens



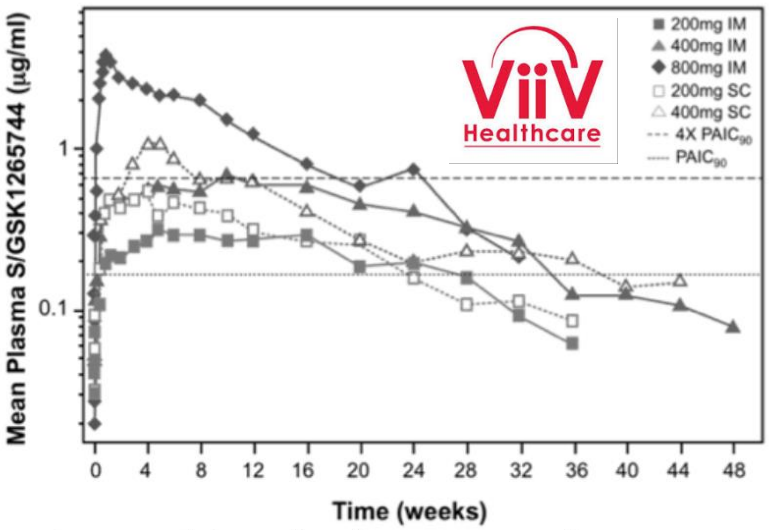
Benefits of long-acting delivery of HIV drugs

Rilpivirine LA (NNRTI)



van 't Klooster *et al. Antimicrob Agents Chemother.* 2010 May;54(5):2042-50.

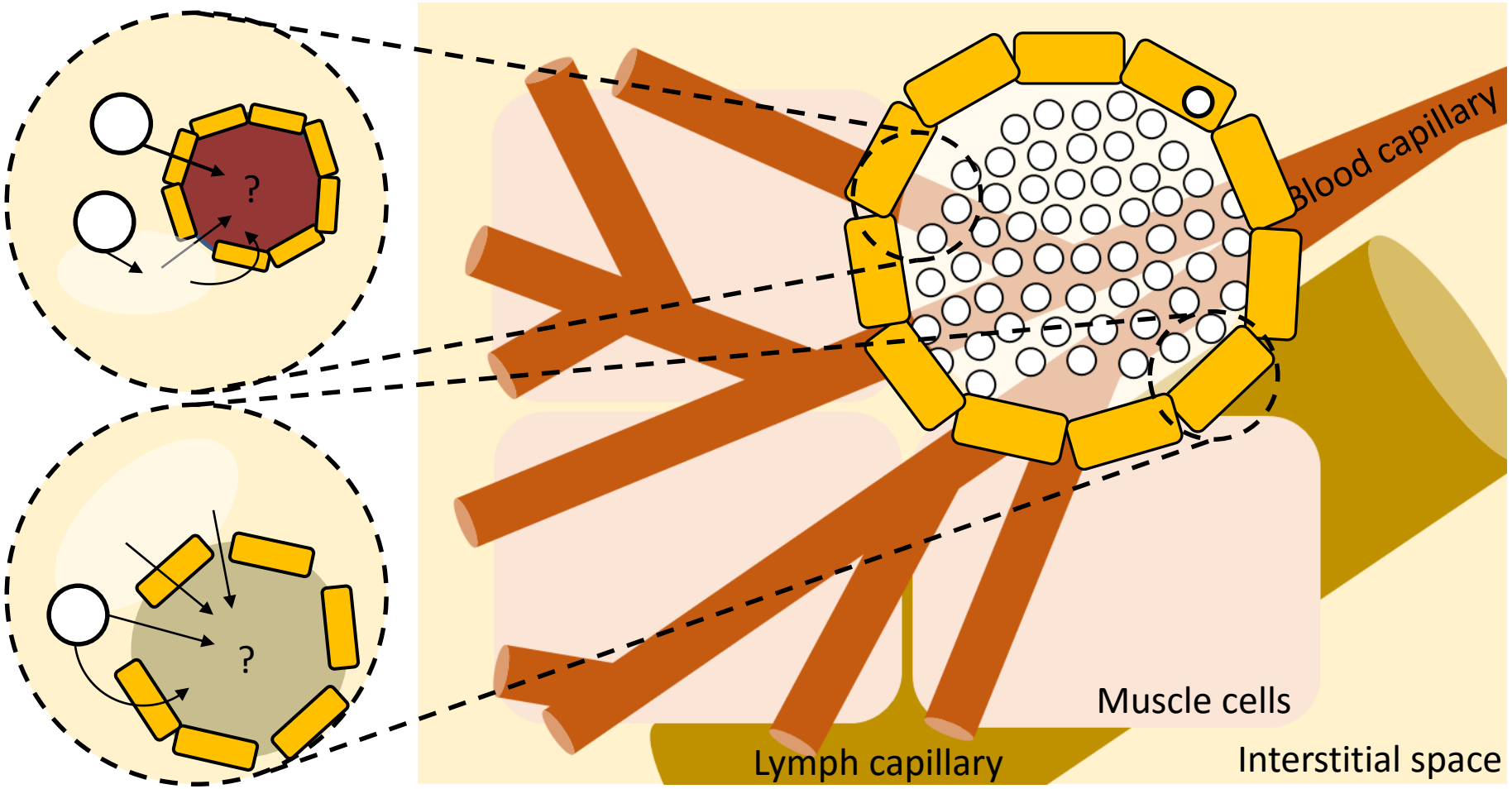
S/GSK1265744 (integrase inhibitor)



Spreen *et al.* (2012) 17th International AIDS Conference. TUPE040

- Potential for once a month (or longer) administration following intramuscular (or subcutaneous) delivery of solid drug nanoparticles
- Potential application in treatment and pre-exposure prophylaxis
- Requires an oral “lead in” to mitigate adverse drug reactions
- Only two drugs currently in development – current limitation for therapy!
- Currently many unanswered questions regarding mechanism for release.

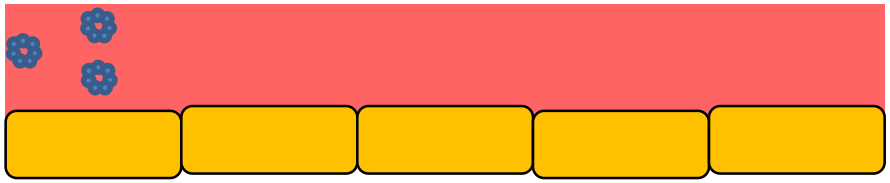
SDNs for long-acting depot delivery of HIV drugs: mechanisms?



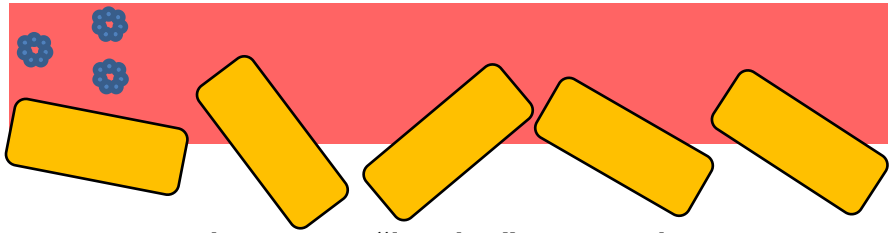
Many unanswered questions regarding what regulates drug release!

Owen and Rannard. ADDR. 2016

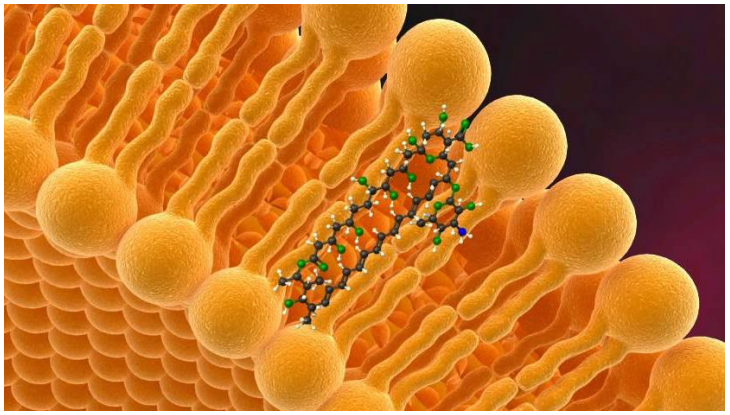
Nanomedicine approaches are almost exclusively driven by a motivation to improve safety

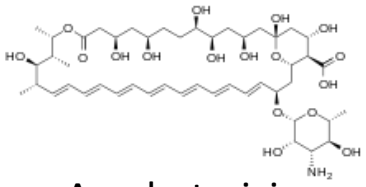


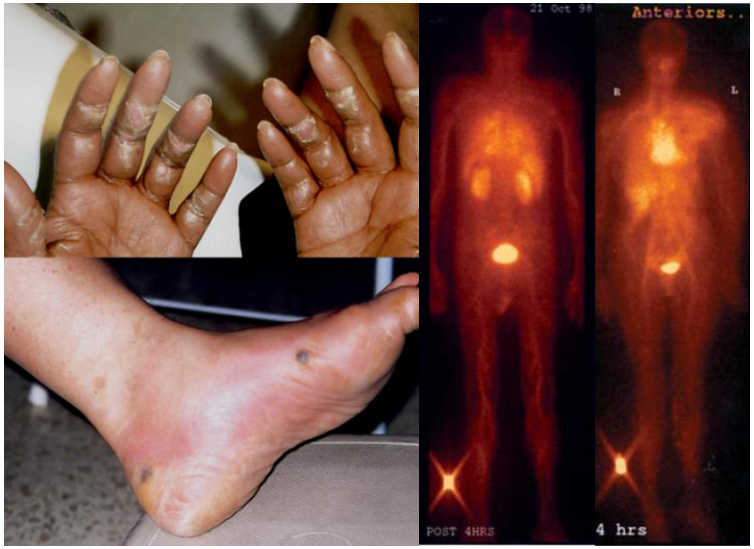
Healthy tissue – normal vasculature

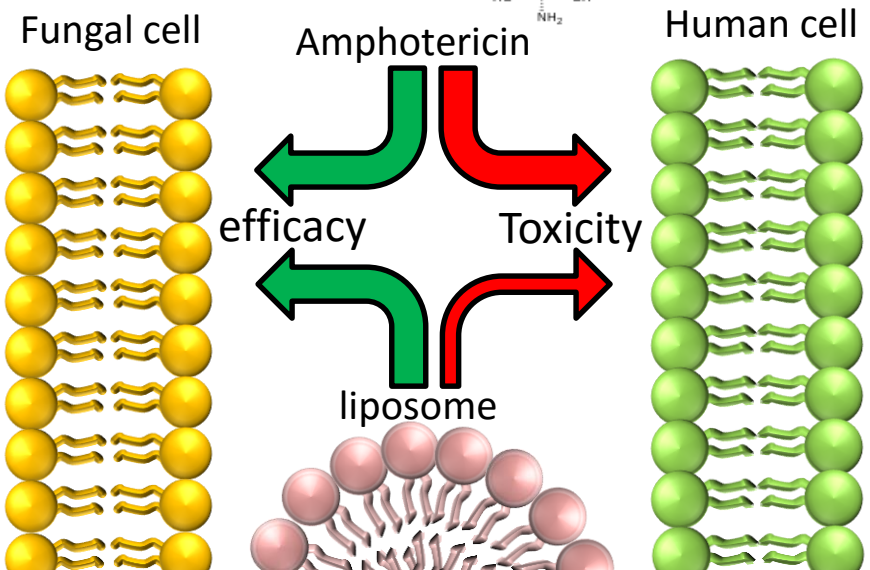


Tumour tissue – “leaky” vasculature









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

Chemical Science

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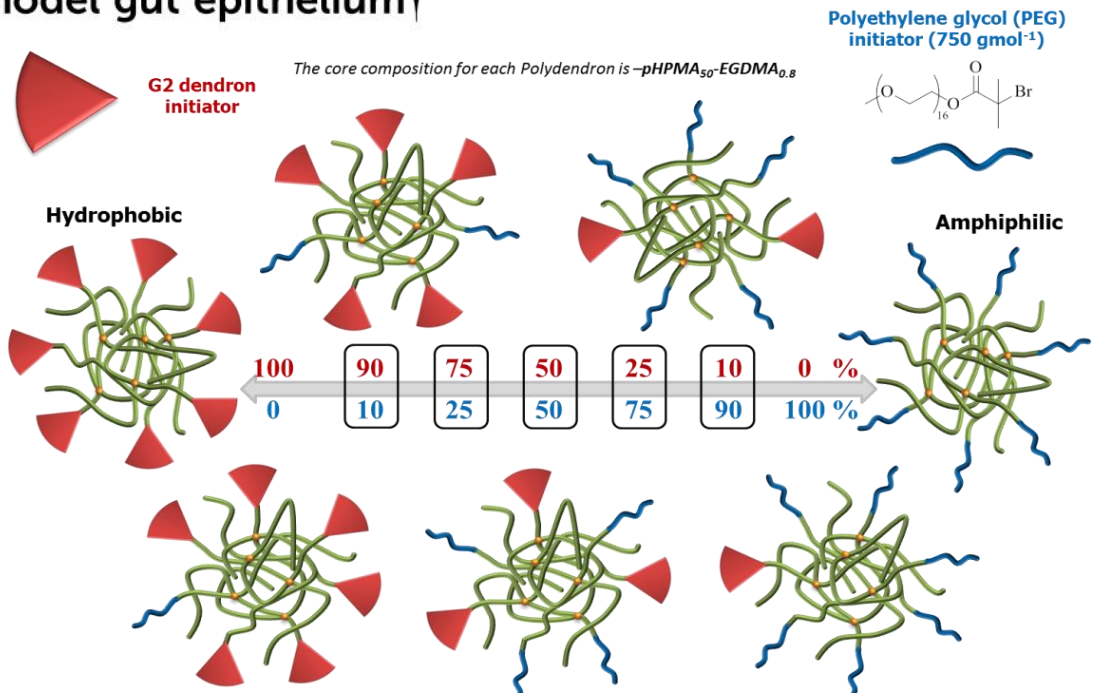
Hyperbranched polydendrons: a new nanomaterials platform with tuneable permeation through model gut epithelium†



Received 19th September 2014
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www.rsc.org/chemicalscience

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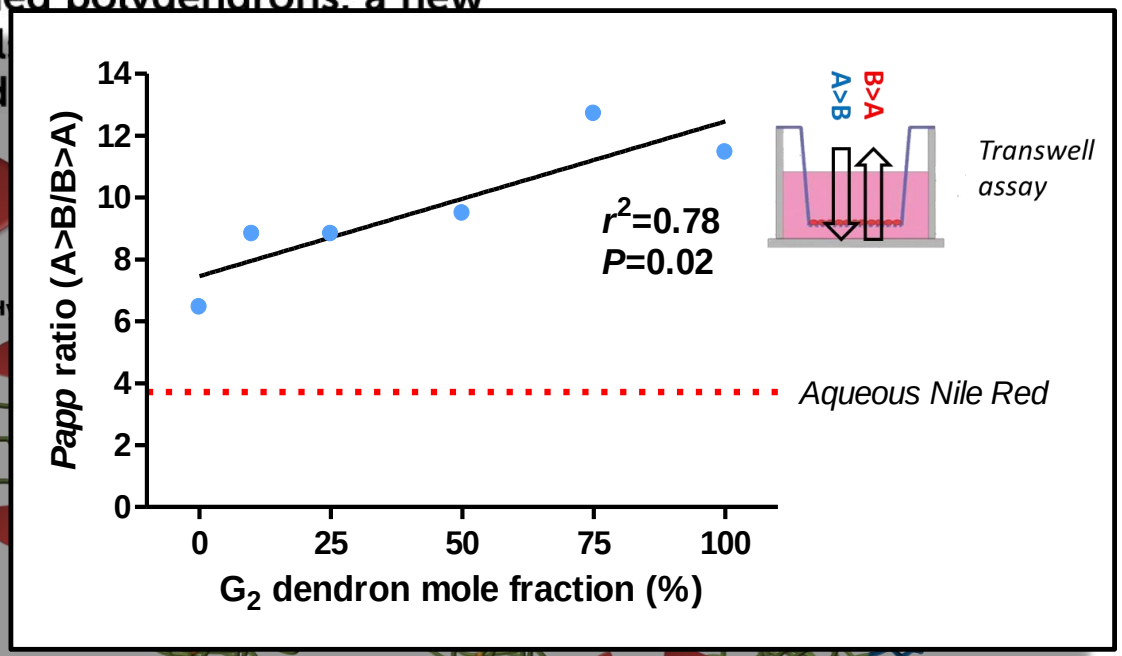

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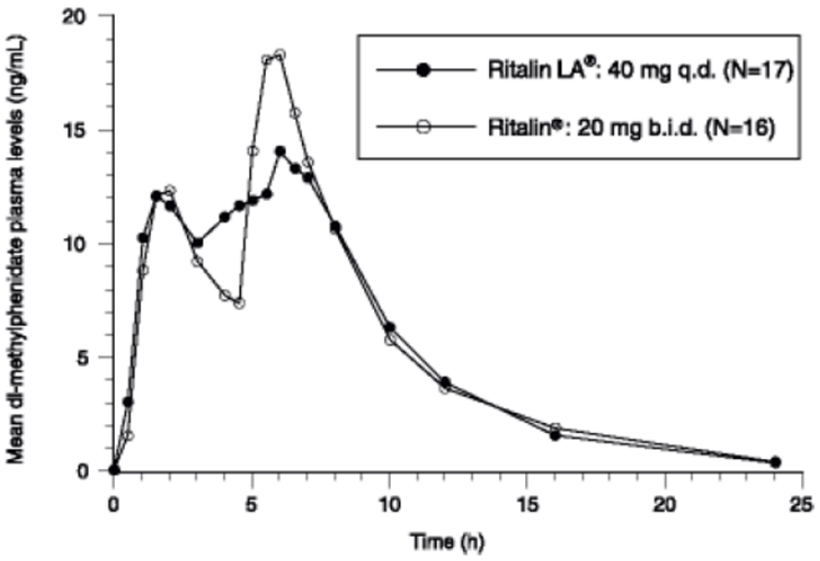
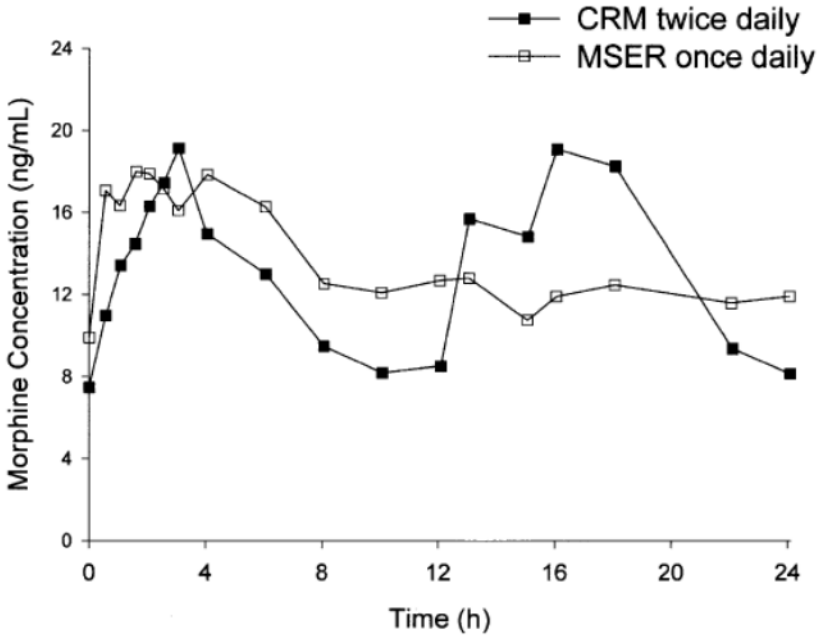
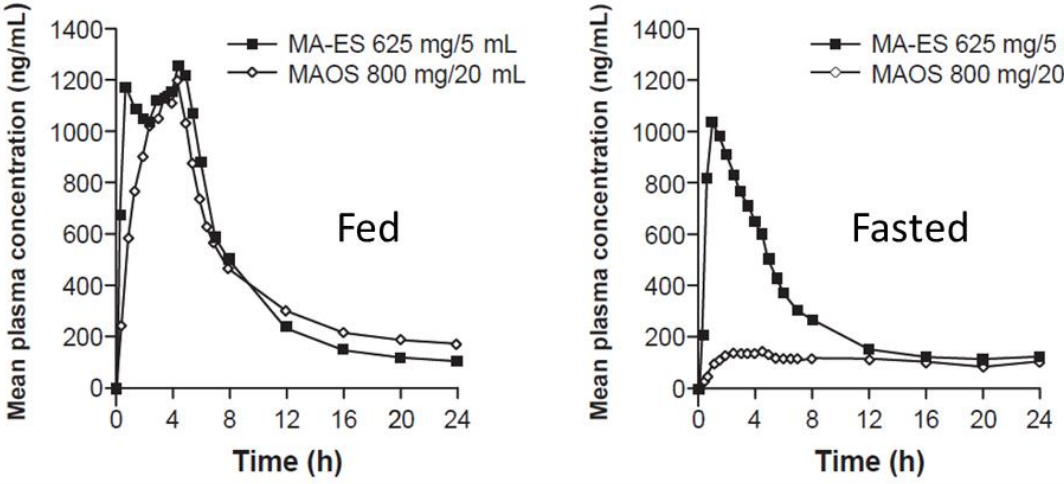
Benefits of SDNs for oral delivery other indications



Haessler *et al. Int J Clin Pharmacol Ther.* 2008 Sep;46(9):466-76.



Portenoy et al. *J Pain Symptom Manage.* 2002 Apr;23(4):292-300.



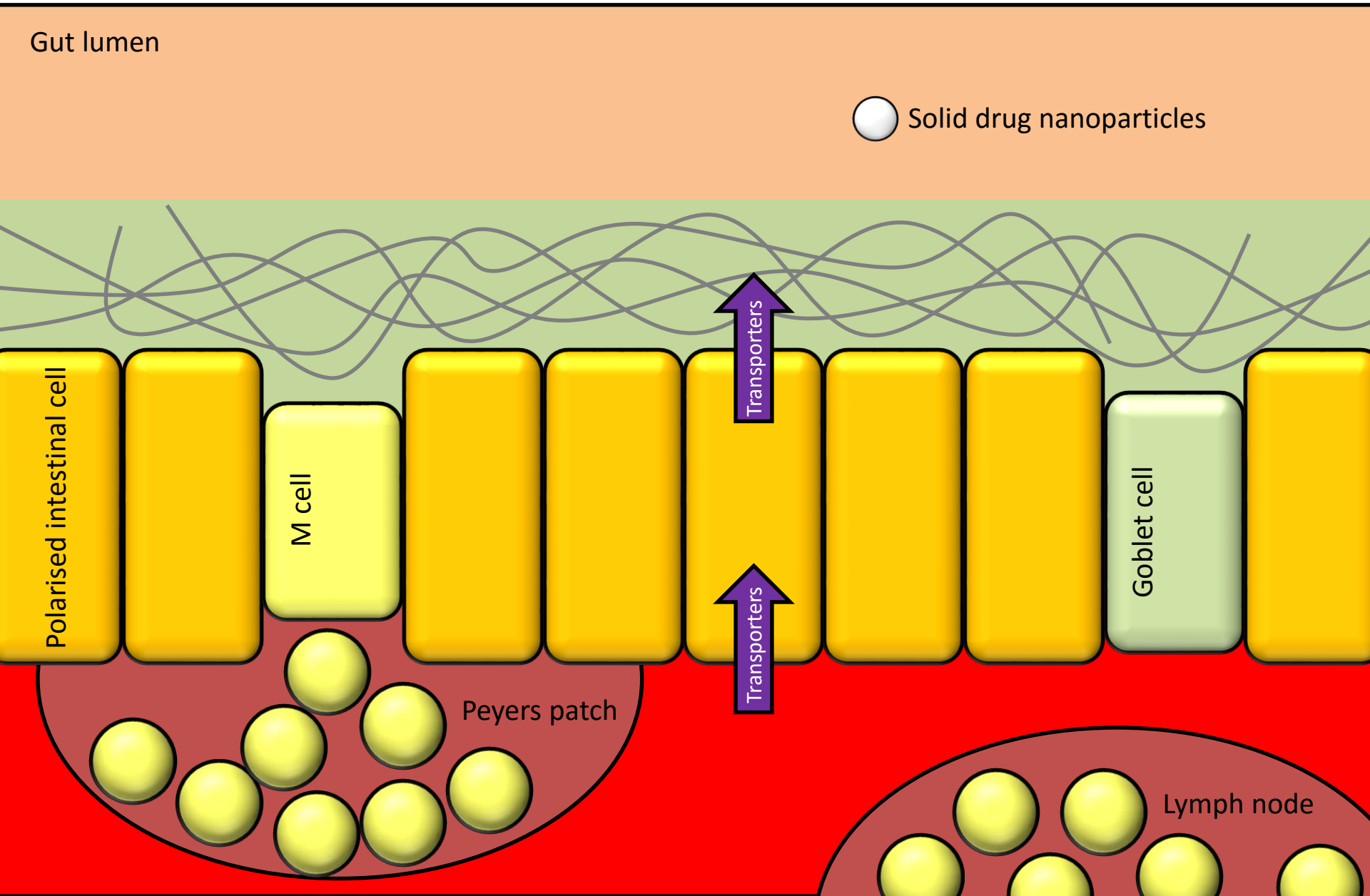
Deschamps *et al. Int J Nanomedicine*. 2009;4:185-92.

Table 1. Pharmacokinetics of single doses of 10 mg dalfampridine (immediate release) and dalfampridine-ER in healthy volunteers.

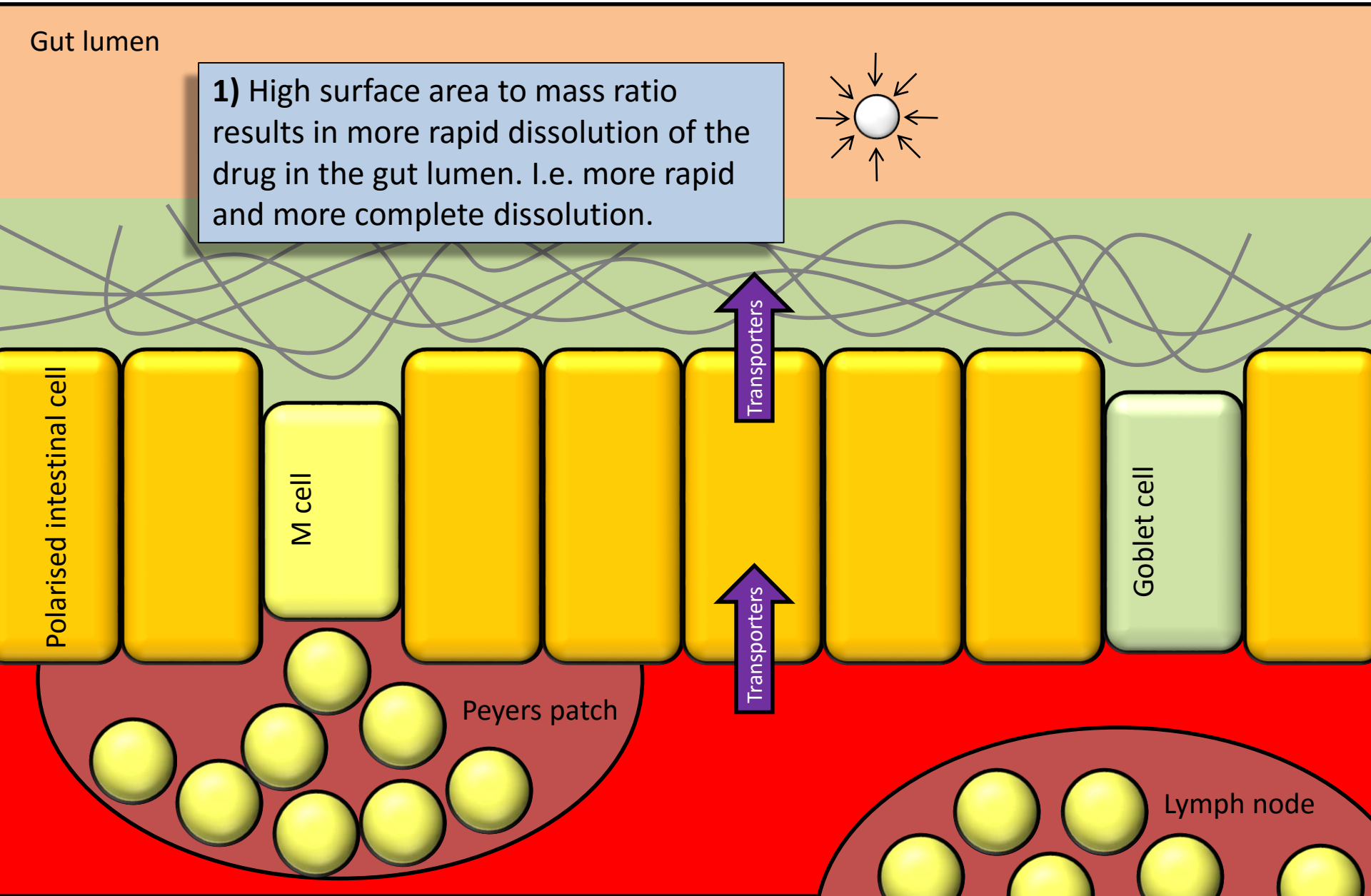
Pharmacokinetic parameter	Mean (SE)	
	Dalfampridine 10 mg ($n=6$)[28]	Dalfampridine-ER 10 mg ($n=5$)[30]
T_{max}, h	1.2 (0.4)	3.2 (0.7)
C_{max}, ng/mL	46.4 (9.7)	21.6 (1.7)
AUC, ng·h/mL	173.1 (26.6)	254.1 (15.7)
$AUC_{0-\infty}$, ng·h/mL	184.6 (24.0)	284.8 (14.2)
Apparent k_e, h^{-1}	0.19 (0.03)	Not estimated
Apparent plasma $t_{1/2}$, h	3.7 (0.7)	6.4 (0.6)
Apparent *CL/F*, mL/min	Not estimated	591.2 (30.3)

Weir *et al. Curr Med Res Opin.* 2013 Dec;29(12):1627-36.

Nanotechnologies and oral drug delivery



Nanotechnologies and oral drug delivery



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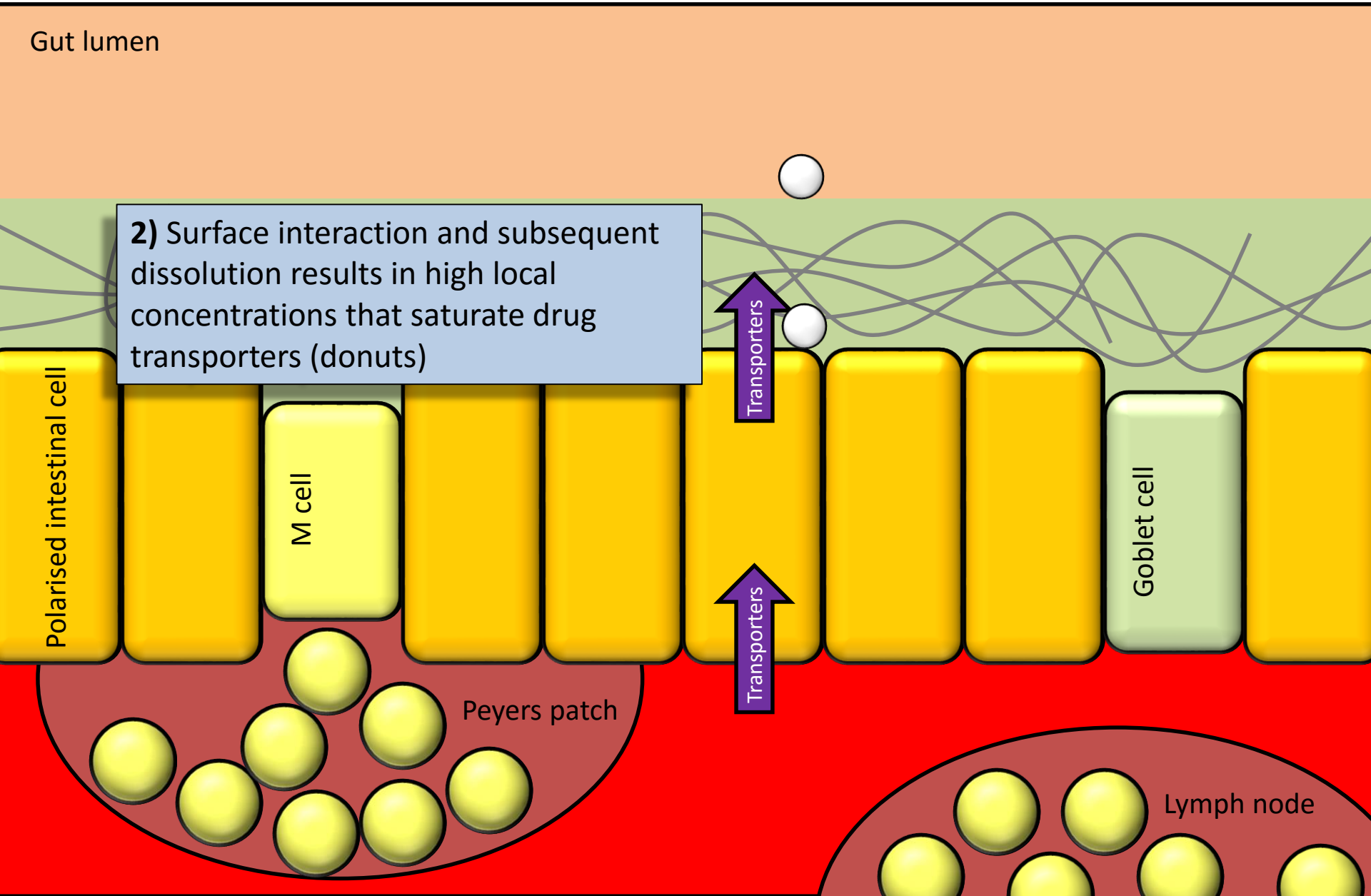

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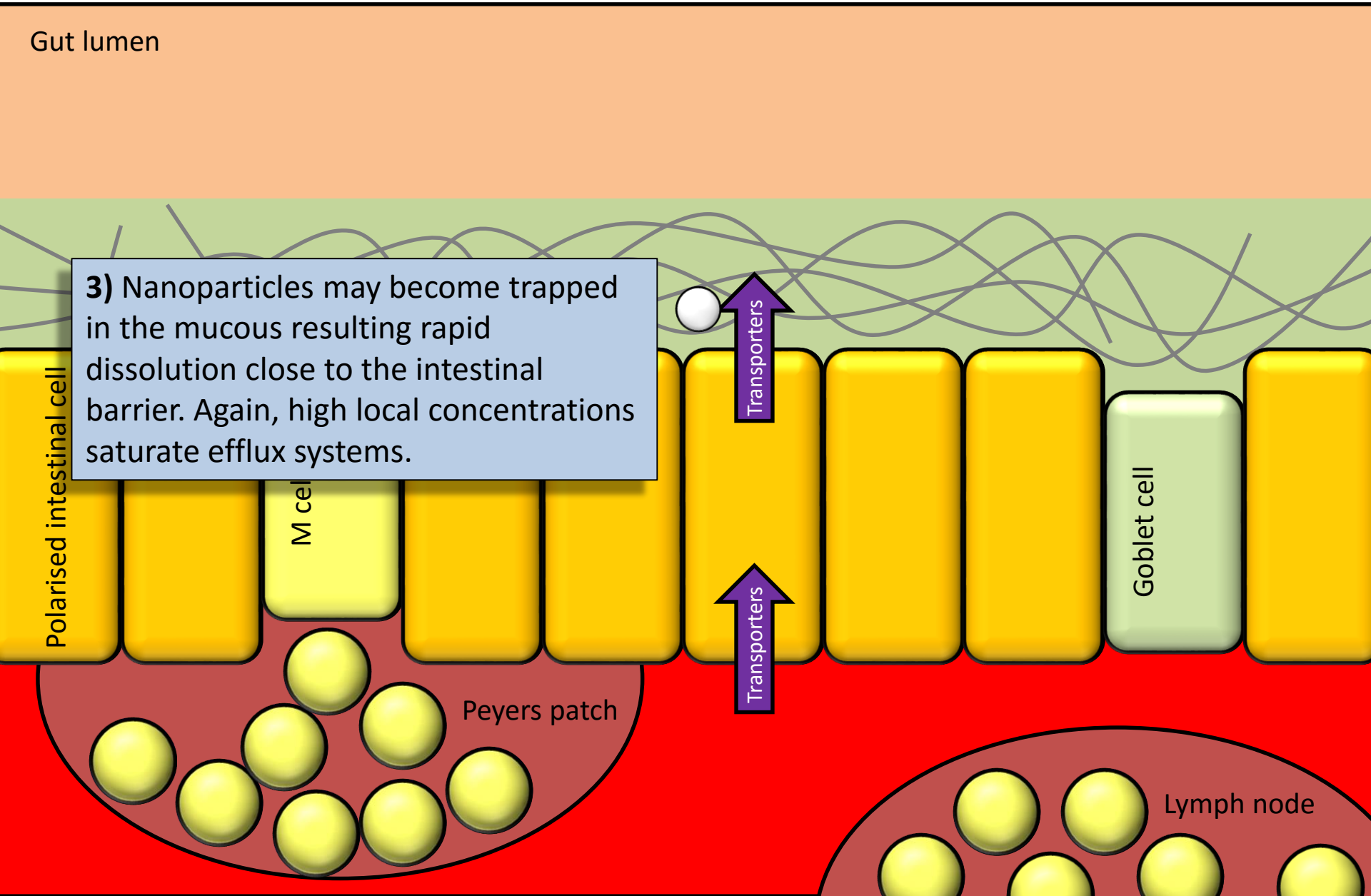
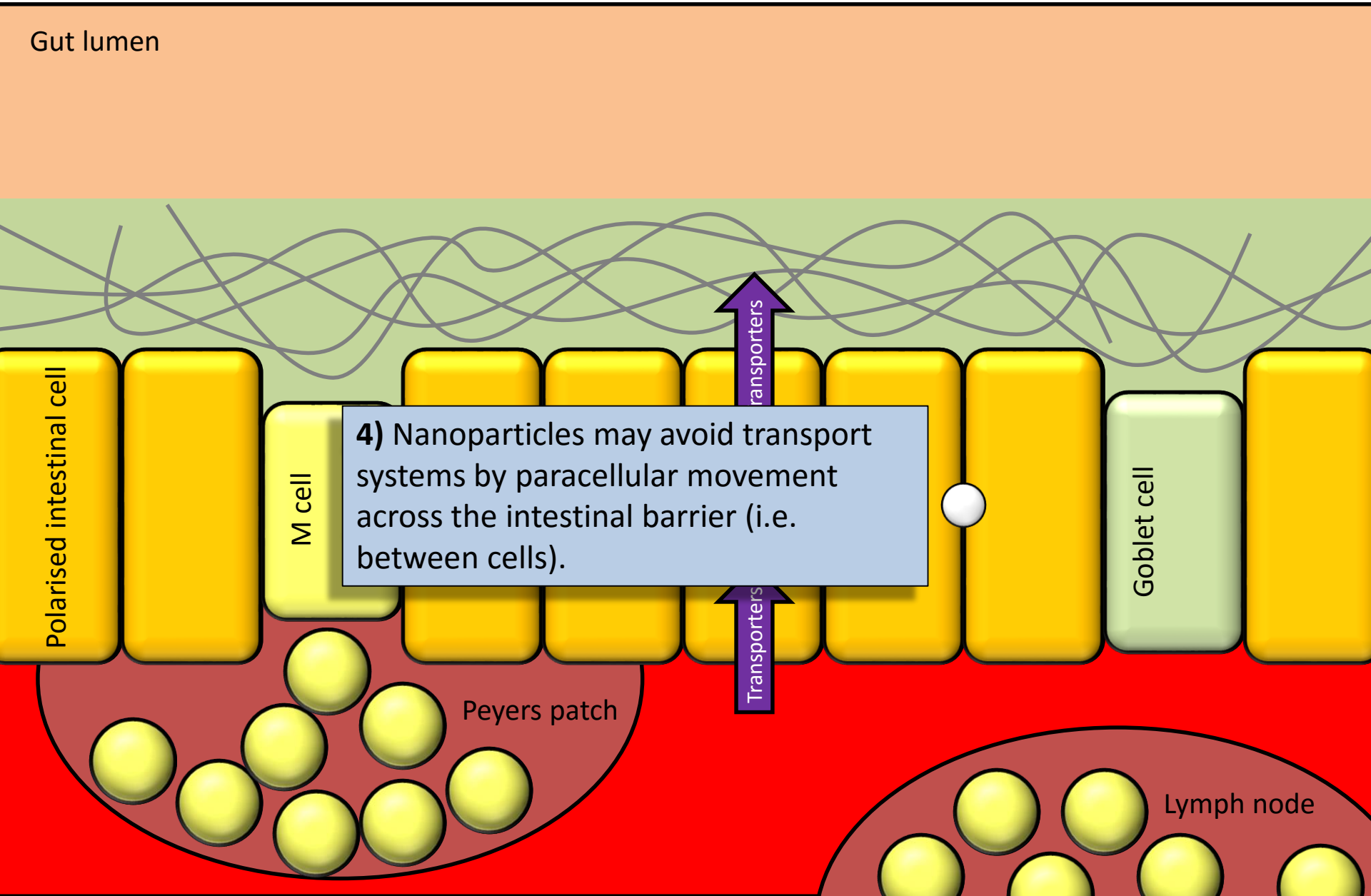


Nanotechnologies and oral drug delivery



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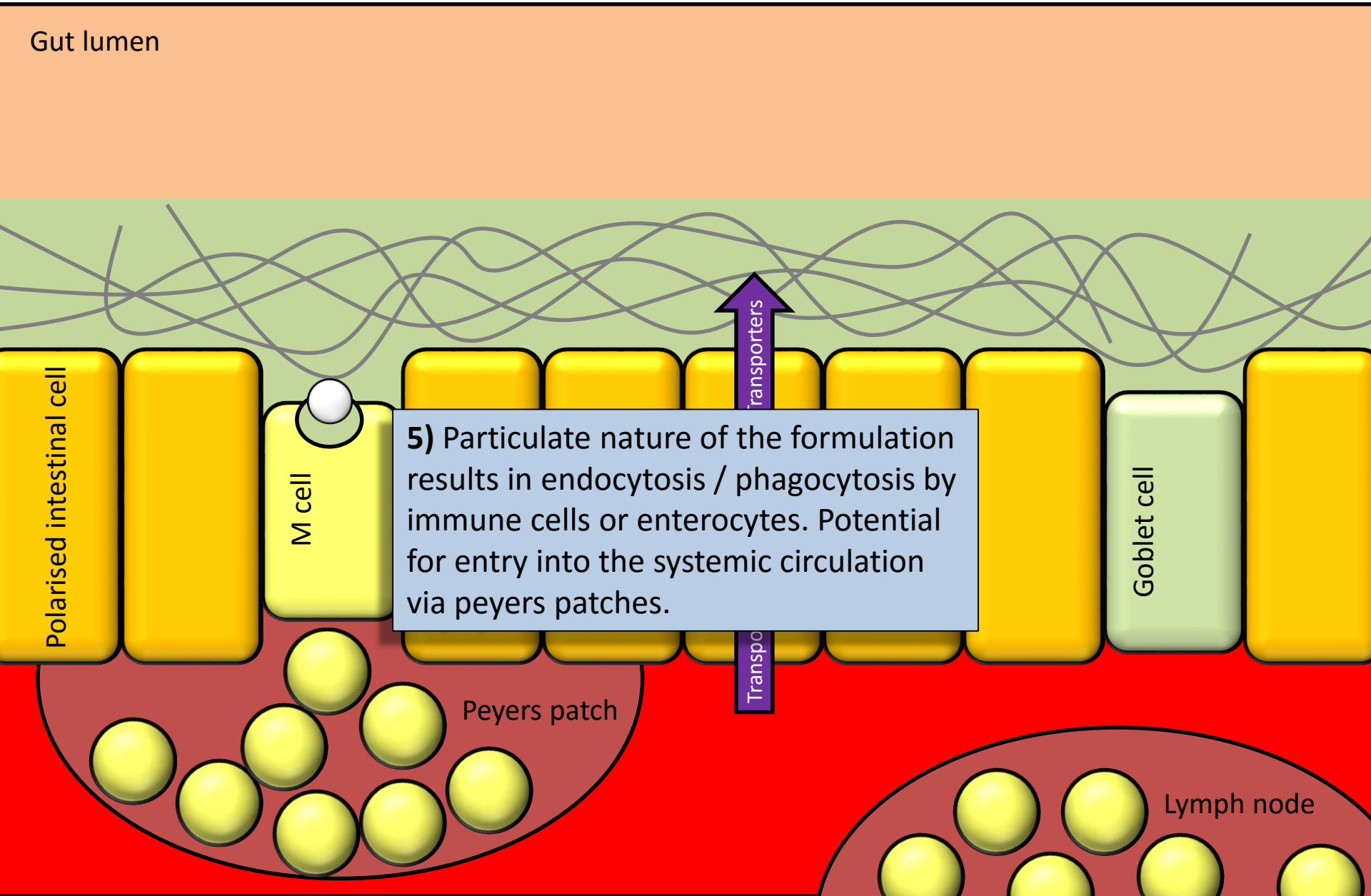
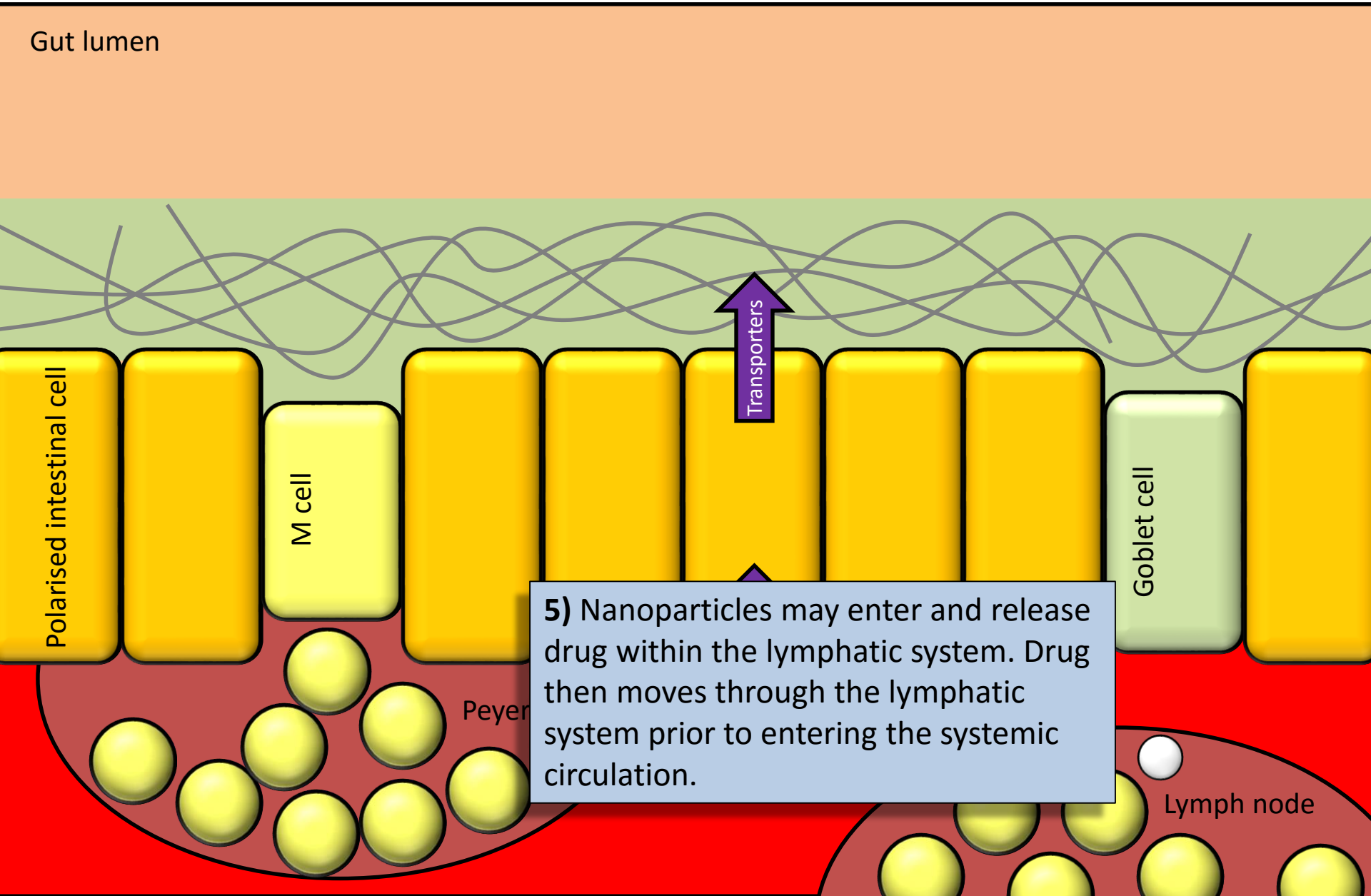
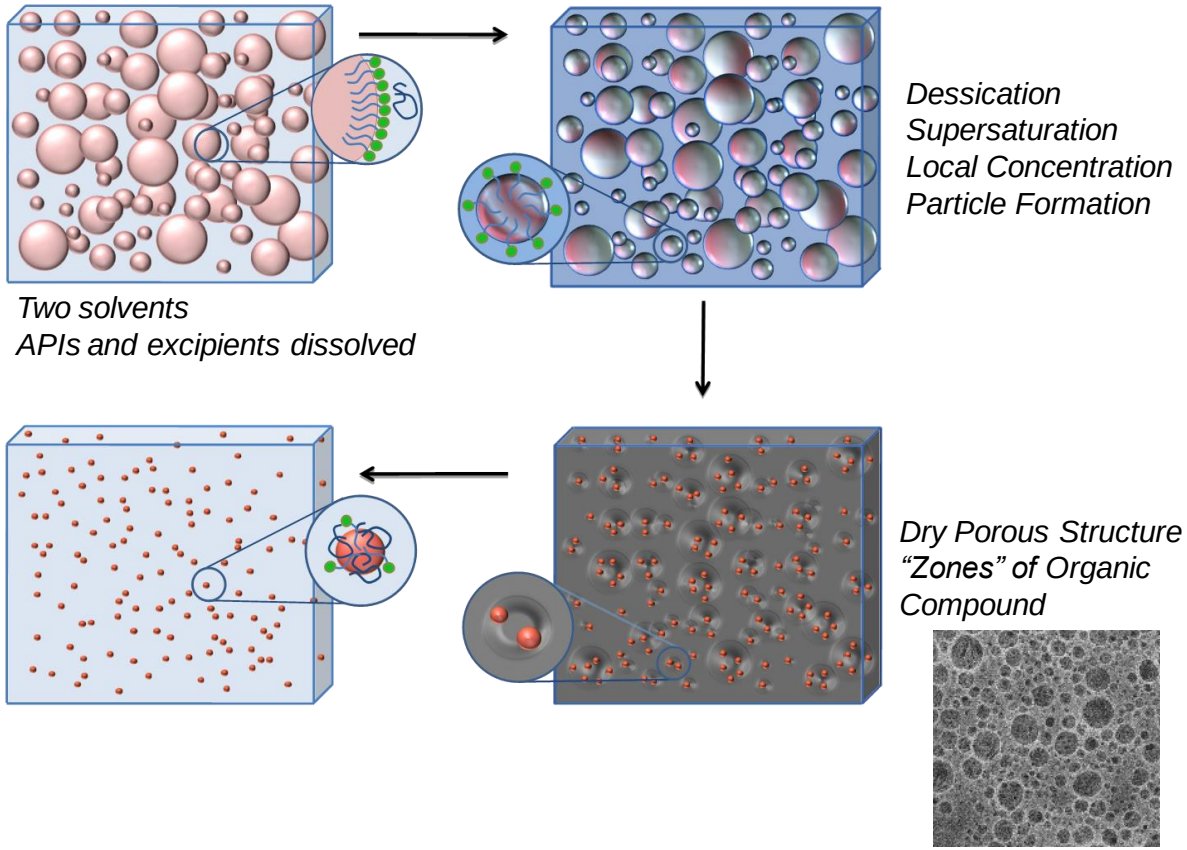


Nanotechnologies and oral drug delivery



Emulsion-templated freeze/spray drying

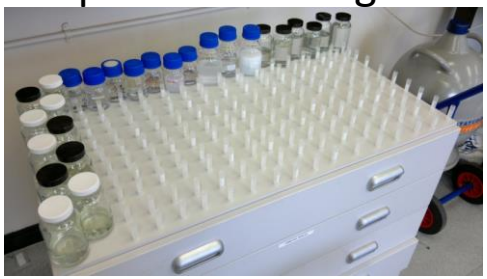
- Generates solid nanosuspensions in one step
- Utilises volatile solvents (freeze drying, spray drying/granulation)



Zhang et al Nature Nanotechnology 3, 2008, 506 – 511

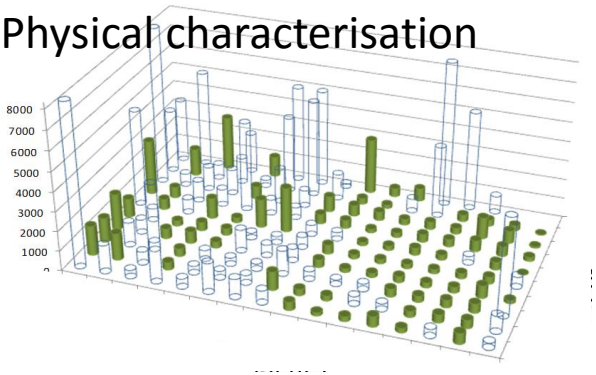
Liverpool multidisciplinary nanomedicine development approach

Excipient screening

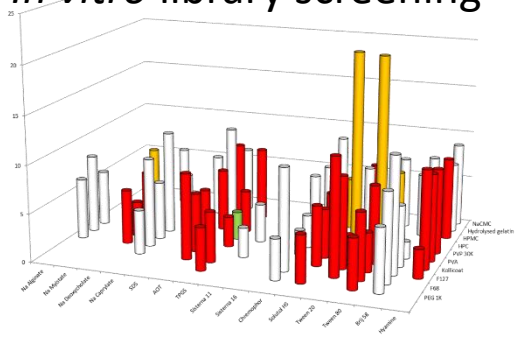


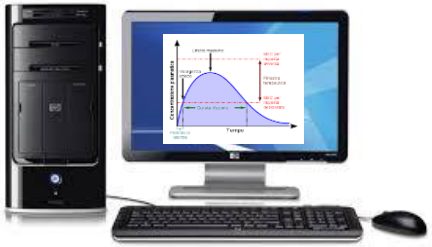
Freeze-dry library

Physical characterisation



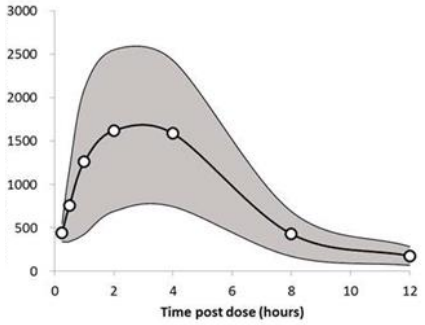
In vitro library screening

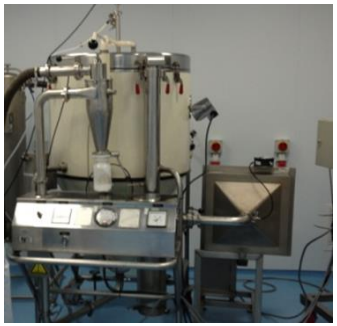




In silico PK prediction

In vivo confirmation





Spray-dry / GMP translation

- Regulatory engagement / approval
- Clinical development (in collaboration with SSAT)
- Market analysis (in collaboration with MPP)
- Tech transfer and industry engagement

Summary of oral antiretroviral solid drug nanoparticle development

- Lead selection from detailed pharmacological investigation (Lopinavir and efavirenz)
- Translated to cGMP production
- Long-term stability established in powder-filled capsules
- Regulatory approval of IMPDs and ethical approval of clinical protocol are now in place
- First patient enrolled in December 2015 (EudraCT number 2013-004913-41)

EUNCL
Nanomedicine Characterisation Laboratory

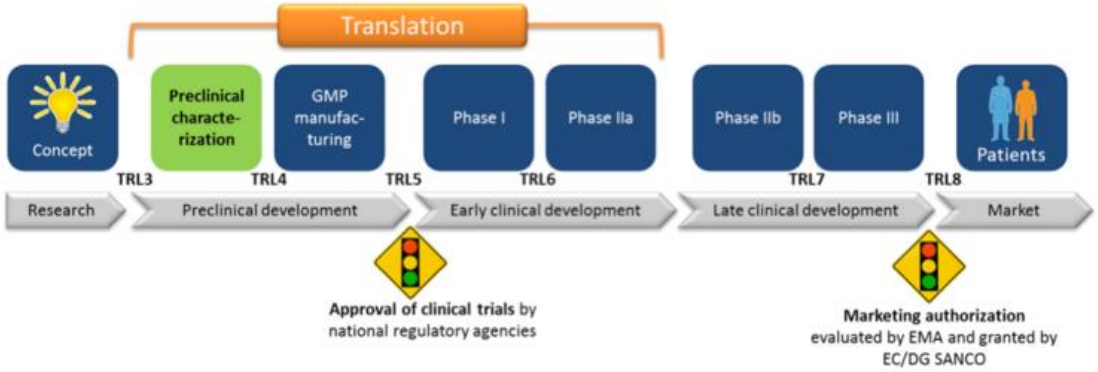
EU-NCL

European Nanomedicine Characterisation Laboratory

Our Mission is:

- To provide a trans-disciplinary testing infrastructure covering a comprehensive set of preclinical characterisation assays (physical, chemical, *in-vitro* and *in-vivo* biological testing) allowing researchers to fully comprehend the biodistribution, metabolism, pharmacokinetics, safety profiles and immunological effects of their Med-NPs.
- To foster the use and deployment of standard operating procedures (SOPs), benchmark materials, and quality management for the preclinical characterisation of Med-NPs (nanoparticles used for medical applications).

To promote inter-sectorial and inter-disciplinary communication among key drivers of innovation, especially between developers and regulatory agencies.



To fulfill its mission EU-NCL aims to achieve 4 major objectives:

Events

European Nanomedicine Meeting (ENM) 2015
7 to 9 December 2015, Grenoble, France

BioNanoMed 2016 - Nanotechnology enables Personalized Medicine
6 to 8 April 2016, Krems, Austria

CLINAM 2016
26 to 29 June 2016, Basel, Switzerland

The Fifth International Conference NANOSAFE 2016
7 to 10 November, Grenoble, France

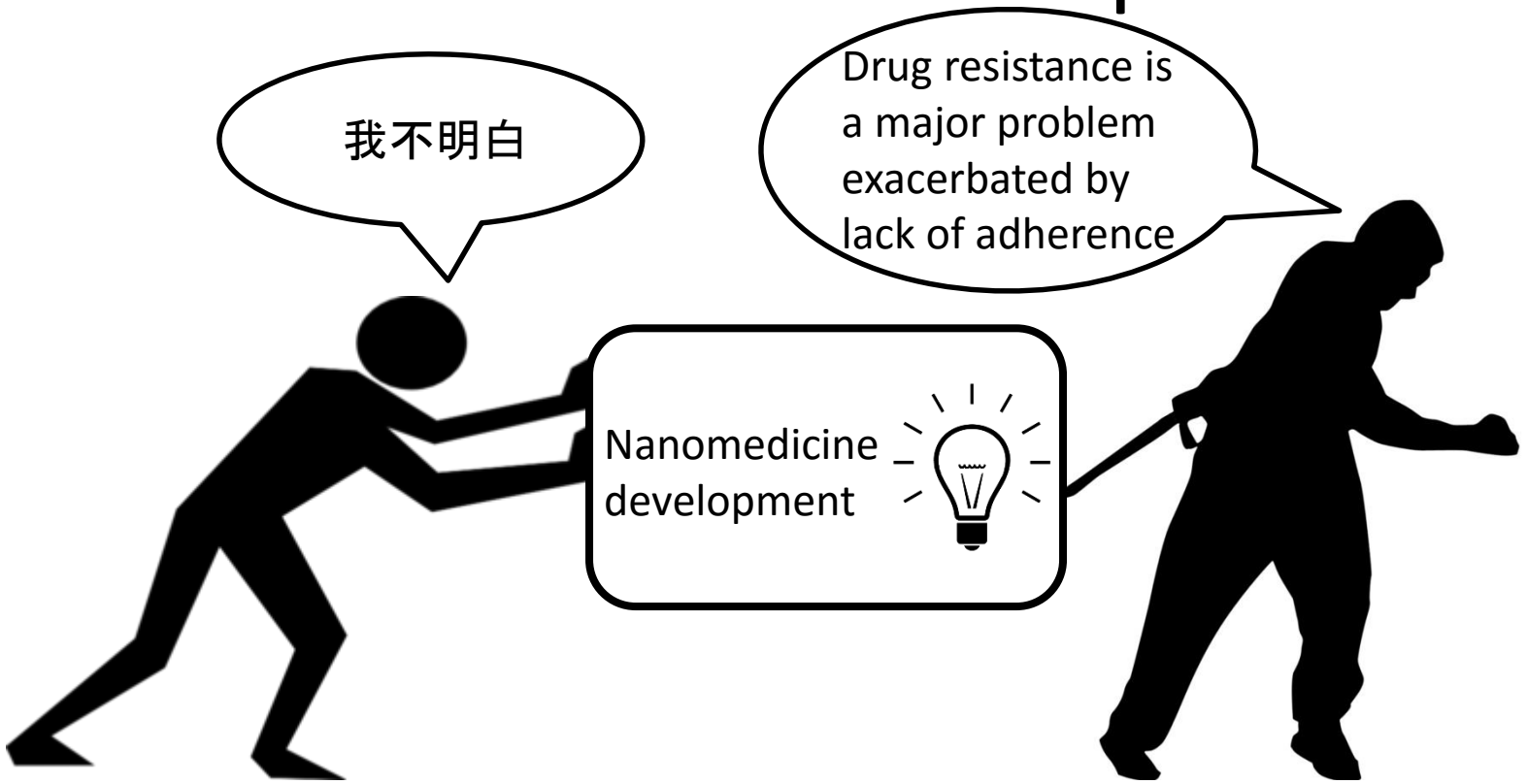
More Events ...

News

EUNCL present at EU-US workshop on H2020
A delegation from EUNCL has been invited to attend an EU-US workshop on H2020, the European Union's main instrument for funding research and innovation activities from 2014 to 2020. Horizon 2020 focuses on three overarching priorities – excellent science, industrial leadership and societal challenges and is open to participants from anywhere in the world.

Cancer in the crosshairs
Switzerland has joined an unprecedented scientific collaboration between Europe and the United States to accelerate nanomedicine testing in a bid to conquer a common enemy: cancer.

Discipline-dependent acceleration of nanomedicine development



Technological push **Clinical pull**

- A worryingly high percentage of nanomedicine candidates have been deemed not suitable for their intended clinical purpose.
- Communication is key to translation of successful new nano-enabled medicines.

Acknowledgements

The Liverpool Team

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Tamara Alhilfi
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