Translation of Nanomedicines to Proof-of-concept in Human

Quality Management Based on Technology Readiness Levels

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External Innovation

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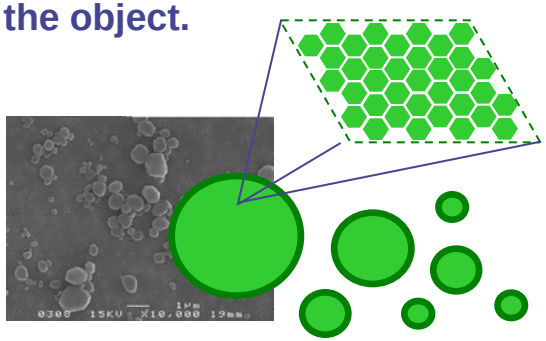
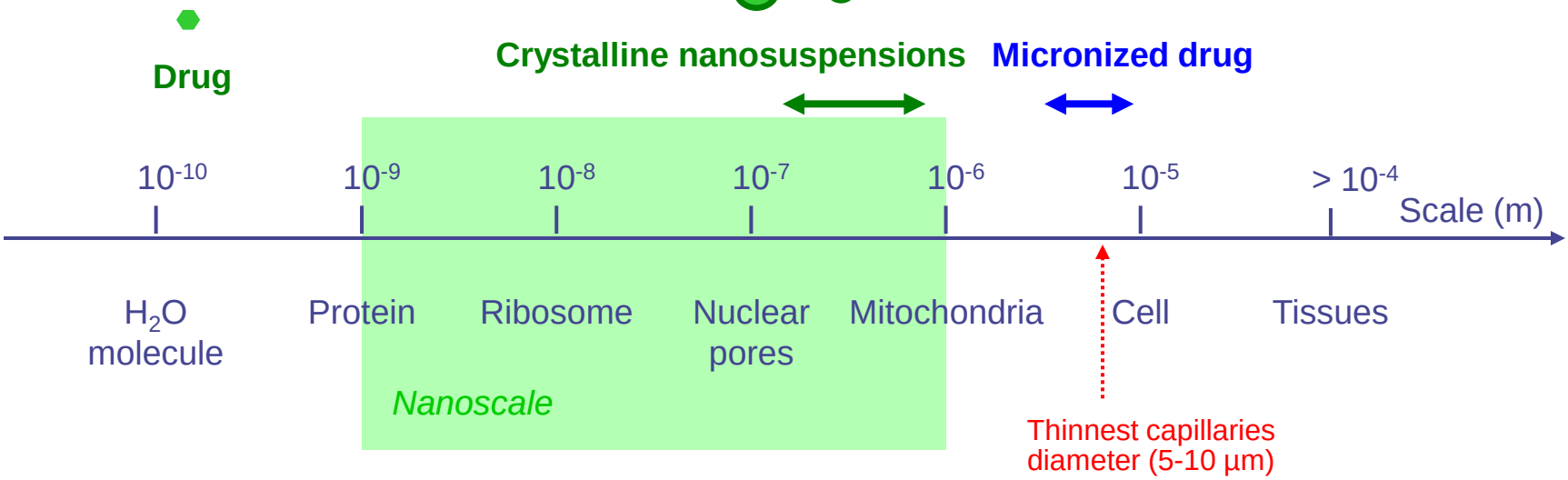
Nanotechnology – A definition

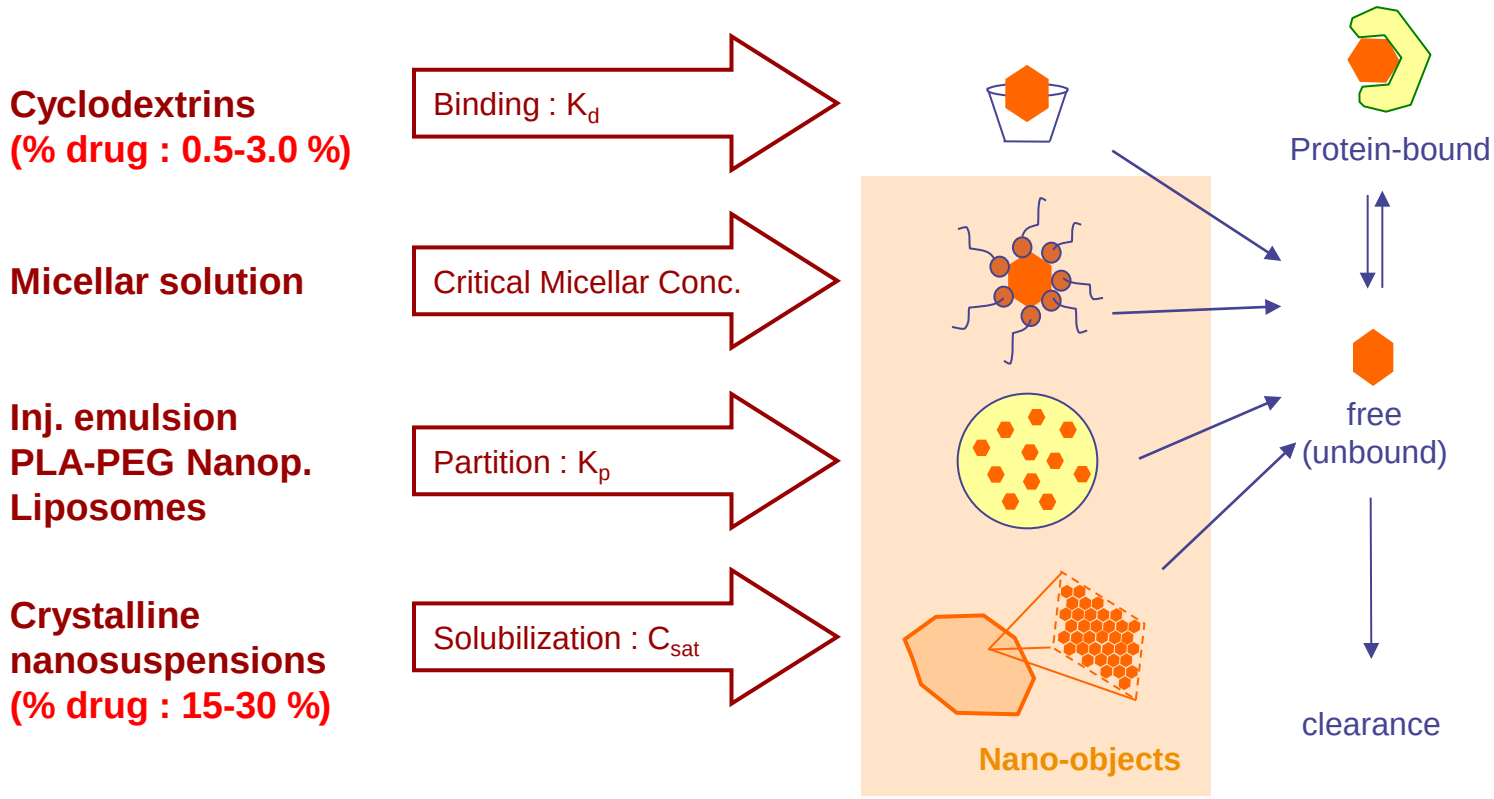
Nanotechnology is the science of designing and producing objects whose size ranges between few nanometers (10^{-9} m) to few hundred of nanometers, as a function of the number of molecules assembled in the object.





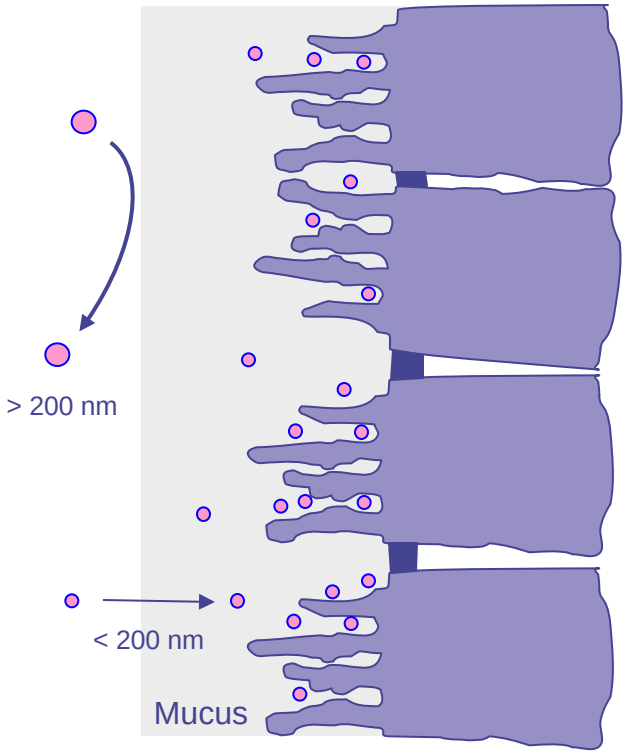
Why small ? (1/2)

- **High level of dispersion - Quick equilibrium shift from dispersed drug to free drug.**



Why small ? (2/2)

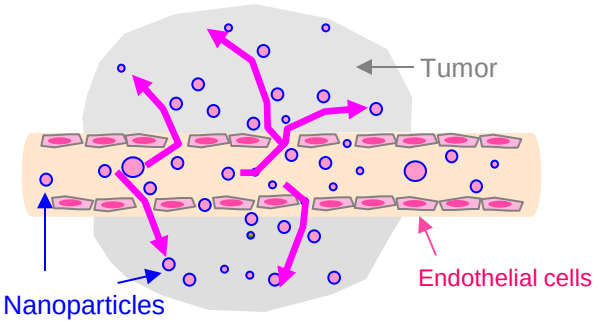
Oral route



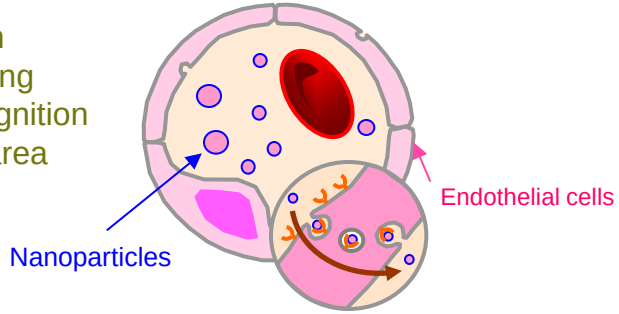
Carry the drug through the mucus in the vicinity of the enterocyte membrane

Intravenous route

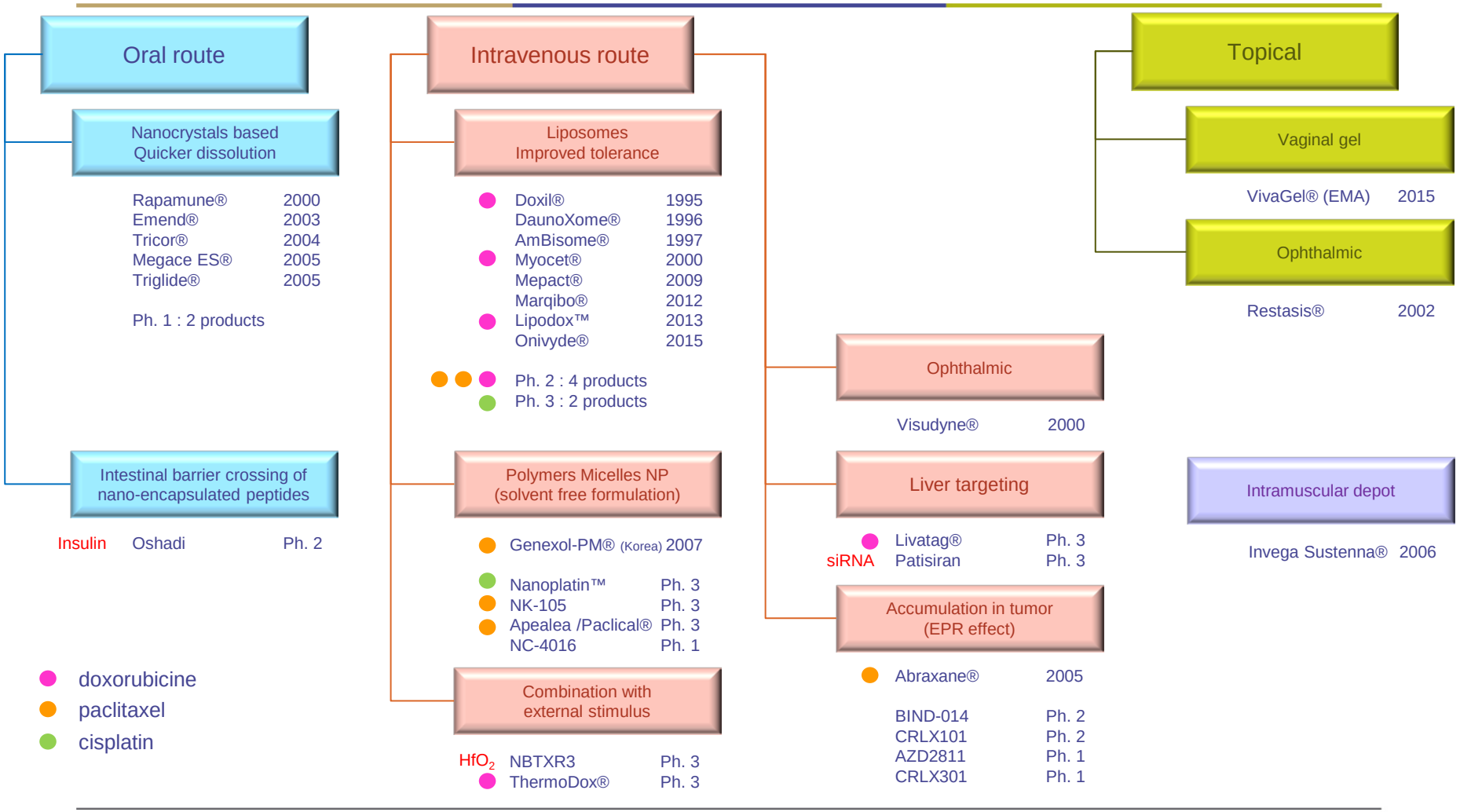
Tumor accumulation (EPR effect)



Blood Brain Barrier crossing through R/L recognition High surface area



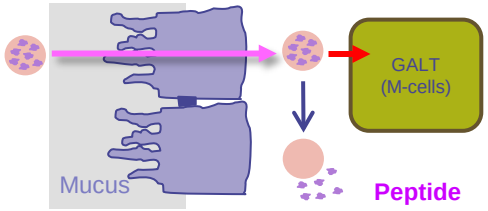
Nanomedicines approved and in development



What makes nanomedicines different from standard formulations ?

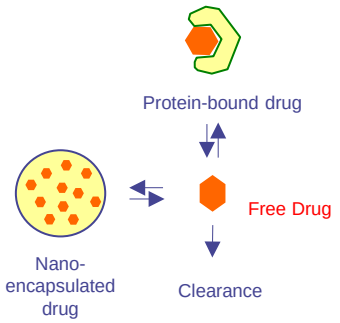
Nanotechnology	Drug Delivery principle(s)	Points to consider
Oral route		
Nano-crystals	Pushing further micronization.	
Intestinal barrier crossing of nano-encapsulated peptides	Protection of the peptides from degradation in the GI fluids. Transport through the intestinal epithelium.	Toxicity and immunogenicity of the nanocarrier having reached the systemic compartment. Relevance of preclinical animal models Dose ranging (exposure vs. dose)

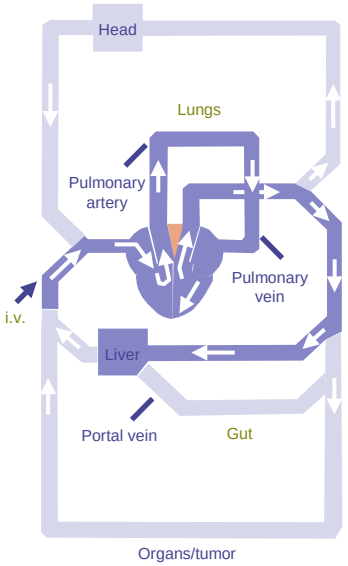
$$\frac{Surface}{Mass} \propto \frac{Surface}{Volume} \propto \frac{1}{diameter}$$



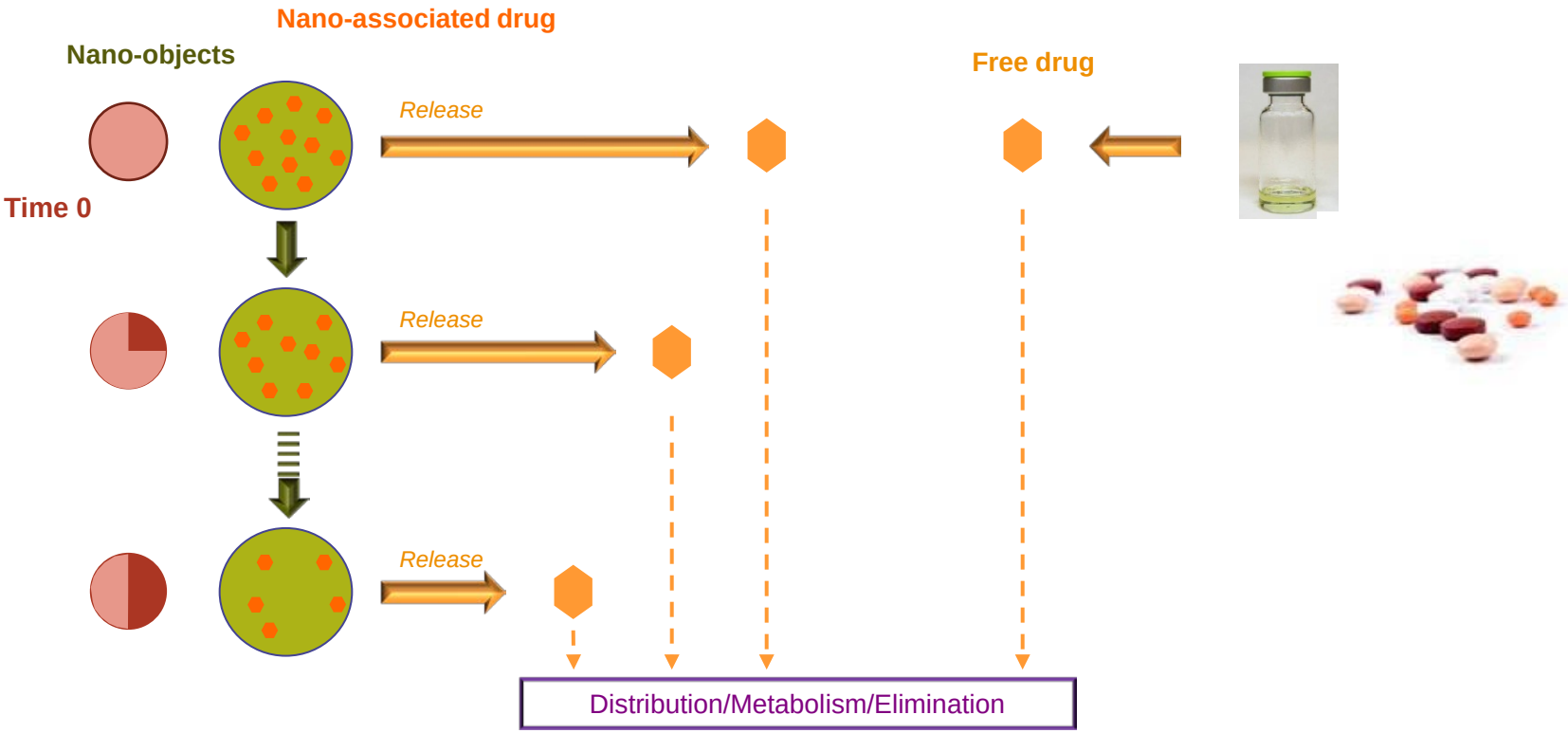
What makes nanomedicines different from standard formulations ?

Nanotechnology	Drug Delivery principle(s)	Points to consider
Intravenous route		
Liposomes, micelles, polymeric nanoparticles	Improved tolerance is based on the diminution of the free fraction of drug.	A particular attention is paid to the fractions of free, protein bound and nano-encapsulated drug.
Accumulation in tumor (EPR effect)	Long circulation of the nanocarrier leads to accumulation of the nano-encapsulated drug in the tumor/	Tumor accumulation versus accumulation is other compartments (liver, spleen). Accumulation kinetics versus release kinetic. Relevance of preclinical animal models. Dose ranging (tumor exposure vs. dose).
Liver targeting	Based on «natural tropism » of nanocarriers for the liver.	« Off target » biological activity. Relevance of preclinical animal models. Immunogenicity.





Why nano-objects are different from standard formulations ?



Regulation on nanomedicines – USA

- Approach
  - Nanomedicines considered within existing guidelines on a product-by-product basis.
  - Manufacturers encouraged to consult with the FDA early in the development process to facilitate mutual understanding.
  - Regulatory science coordination for nanoscale materials:
    - biological interactions, safety assessment,
    - detection (encapsulated and free drug),
    - characterization (National Characterization Laboratory – NIH – Nat. Cancer Institute)
    - Development of *in vitro* and *in vivo* models.
- Documentation
  - General
    - Final Guidance for Industry – Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology.
- Key dates and initiatives
  - March 2008 – FDA/Alliance for NanoHealth scientific workshop (preclinical, clinical, manufacturing),
  - June 2009 – Regulators conference (called by FDA),
  - 2011 – Nanotechnology Assessment Working Group created by the Center for Drug Evaluation and Research (CDER).

Regulation on nanomedicines – European Union

- Approach
  - Nanomedicines considered within existing guidelines on a product-by-product basis
  - Communication by Reflection papers (originated by EMA) and articles.
- Documentation
  - General
    - Reflection paper on nanotechnology based medicinal products for human use (EMEA/CHMP/79769/2006),
    - Next-generation nanomedicines and nanosimilars: EU regulators' initiatives relating to the development and evaluation of nanomedicines.
  - Specific (to address generic products comparability)
    - Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product (EMA/CHMP/SWP/80658/2009 and EMA/CHMP/806058/2009/Rev. 02),
    - Reflection paper on non-clinical studies for generic iron medicinal product applications (EMA/CHMP/SWP/100094/2011),
    - Joint MHLW/EMA reflection paper on the development of block copolymer micelle medicinal products (EMA/CHMP/13099/2013),
    - Reflection paper on surface coatings: general issues for consideration regarding parenteral administration of coated nanomedicine products (EMA/325027/2013).

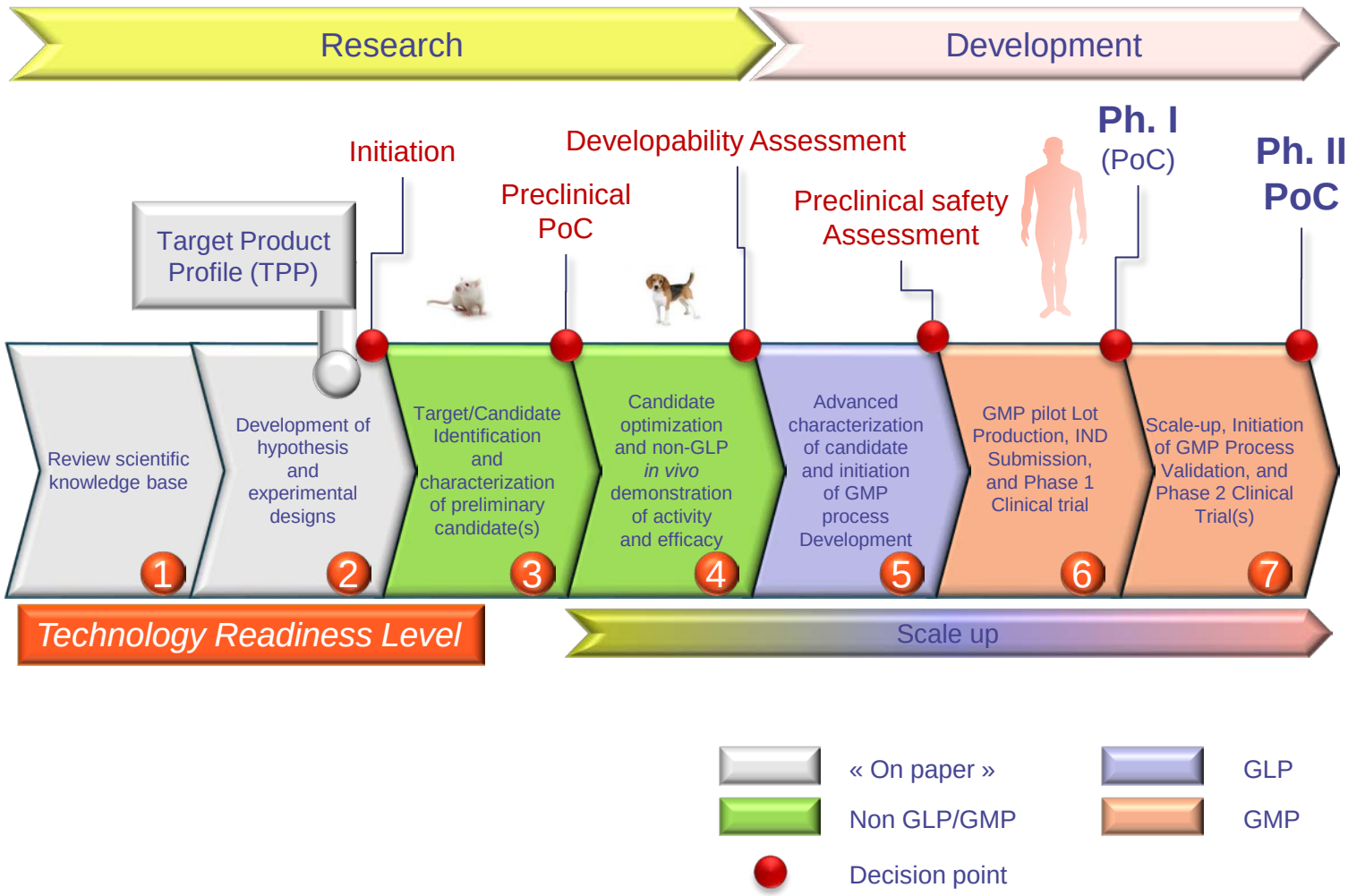
Regulation on nano-medicines – European Union

- Key dates and initiatives
  - 2006 – Creation of a cross-agency Nanomedicine Expert Group.
  - 2009 – CHMP established an ad-hoc expert group on nanomedicines.
  - 2009 – Creation of the International Regulators Subgroup on Nanomedicine, initiative jointly launched by the EU (European Medicines Agency), USA (US FDA), Japan (Ministry of Health, Labour and Welfare) and Canada (Health Canada).
  - Sept. 2010 – International scientific workshop hosted by EMA.
  - 2011 – Creation of a Multidisciplinary expert group on nanomedicines to
    - provide scientific input,
    - collate the current regulatory reflection for the safe approval of nanosimilar nanomedicines.
  - May 2013 – Horizon 2020 white paper European technology Platform on Nanomedicine.
  - 2013 – Nanosimilars (article from EMA in Nanomedicine).
  - 2015 – Creation of the European Nanotechnology Characterization Laboratory.

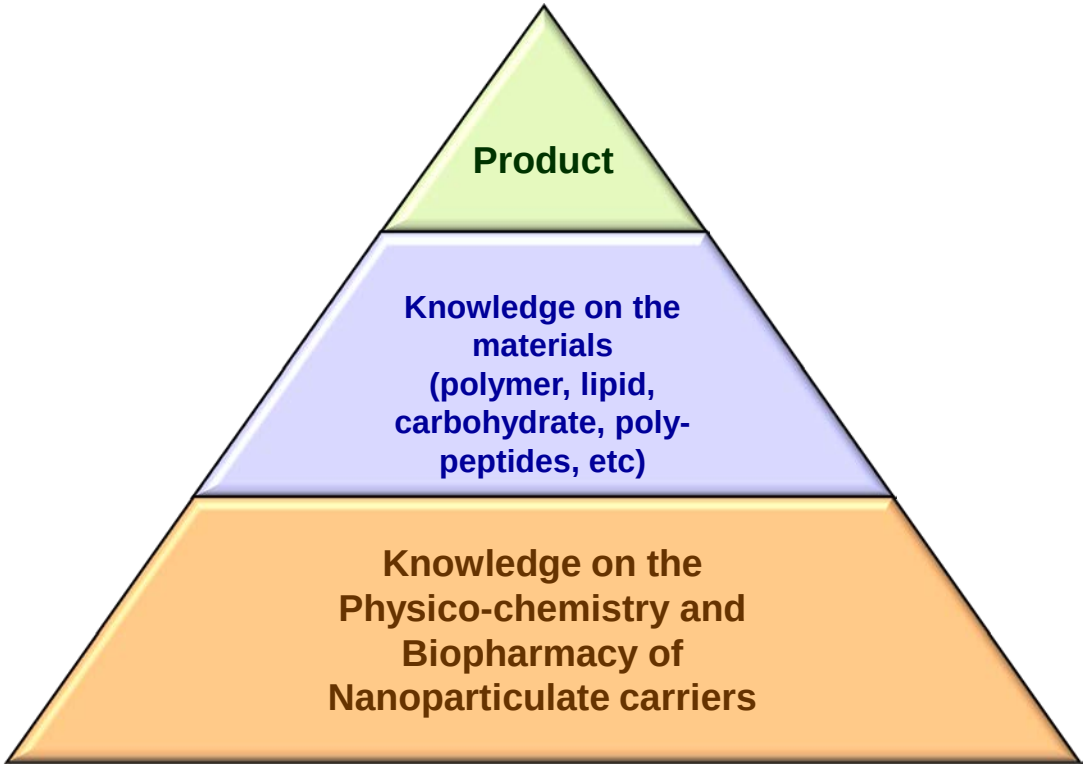
A tentative definition of a « translational approach »

- Parallel elaboration of
  - the product design (drug, drug delivery technology, dose, regimen),
  - the quality by design (QbD) principles (including scale-up),
  - the regulatory strategy (on a product-by-product basis).
- Comparison with the existing treatment and/or alternatives
- De-risking approach
  - identify (and address) methodological gaps: dose ranging (exposure/efficacy/safety), extrapolation of animal data to human, relevance of the preclinical disease model(s),
  - existing regulatory environment and expected changes.
- Computerized integration of release kinetic (k_r) and PK ($T_{1/2}$)
  - Physiologically Based PK (PBPK) models,
  - influence of payload, dose on PK parameters.
- Stepwise investments
  - data packages (validation level of data)
  - value creation (translatability to human)
- Roadmap up to PoC in human (anticipated clinical endpoints)
- Further (full) Development strategy (from PoC in human to commercial product)

Technology Readiness Levels (TRL)



Building blocks of nano-objects quality



TRL 2
- Product profile
- Drug delivery challenge
- Dose ranging

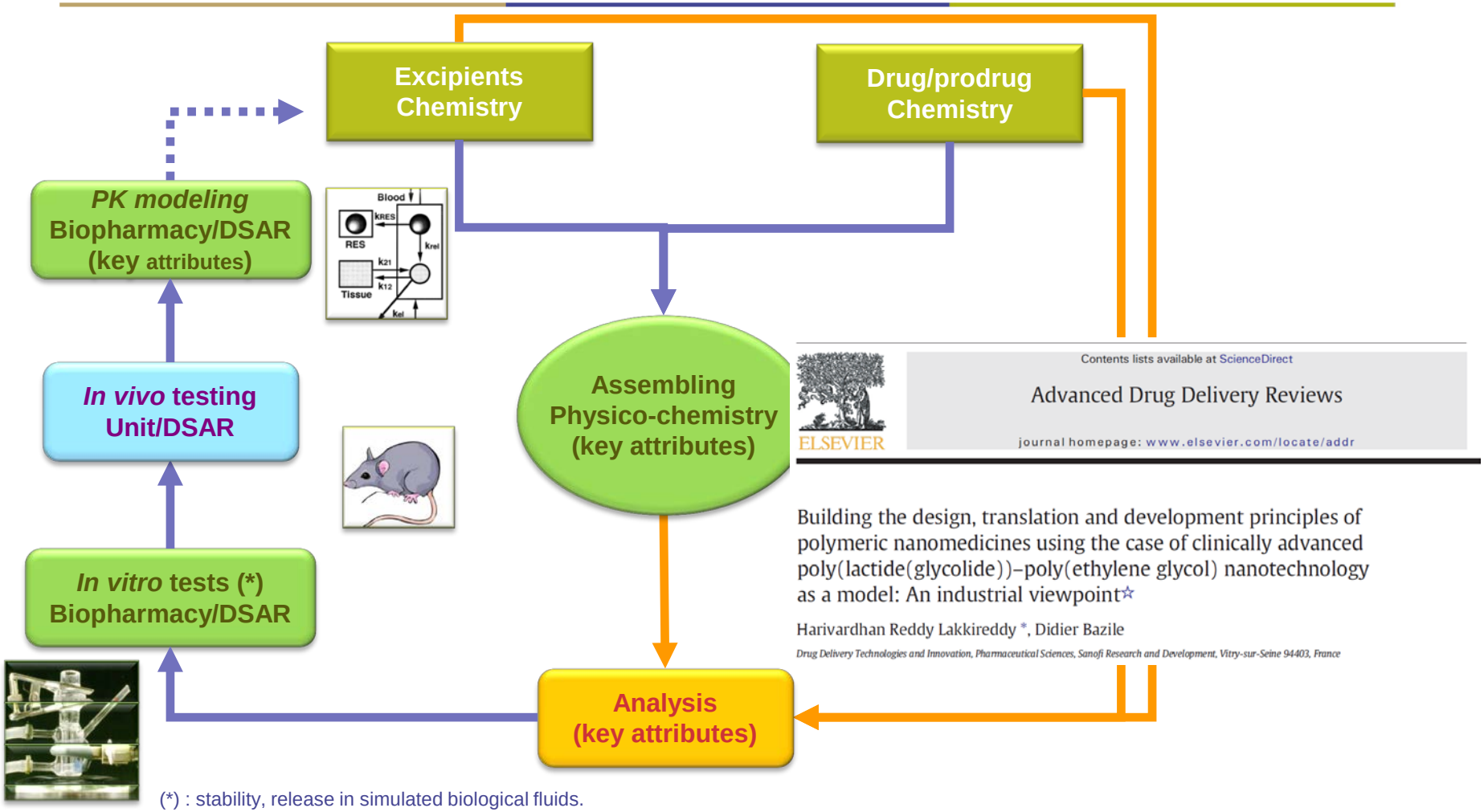
TRL 1
- Physico-chemistry of assembling and encapsulation/release,
- Stability in biological fluids,
- Physico-chemistry/biopharmacy relationships

TRL 1
- Constraints of the administration route,
- Anticipated “desired” and “undesired” accumulation.

From Bazile, D.V. Nanotechnologies in drug delivery – An industrial perspective. J. DRUG DEL. SCI. TECH., 24 (1) 12-21 2014

Pharmacy – Science of drug/excipient(s) assembling

Preclinical proof of concept (TRL 3-4)



Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

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

ELSEVIER

Building the design, translation and development principles of polymeric nanomedicines using the case of clinically advanced poly(lactide(glycolide))–poly(ethylene glycol) nanotechnology as a model: An industrial viewpoint☆

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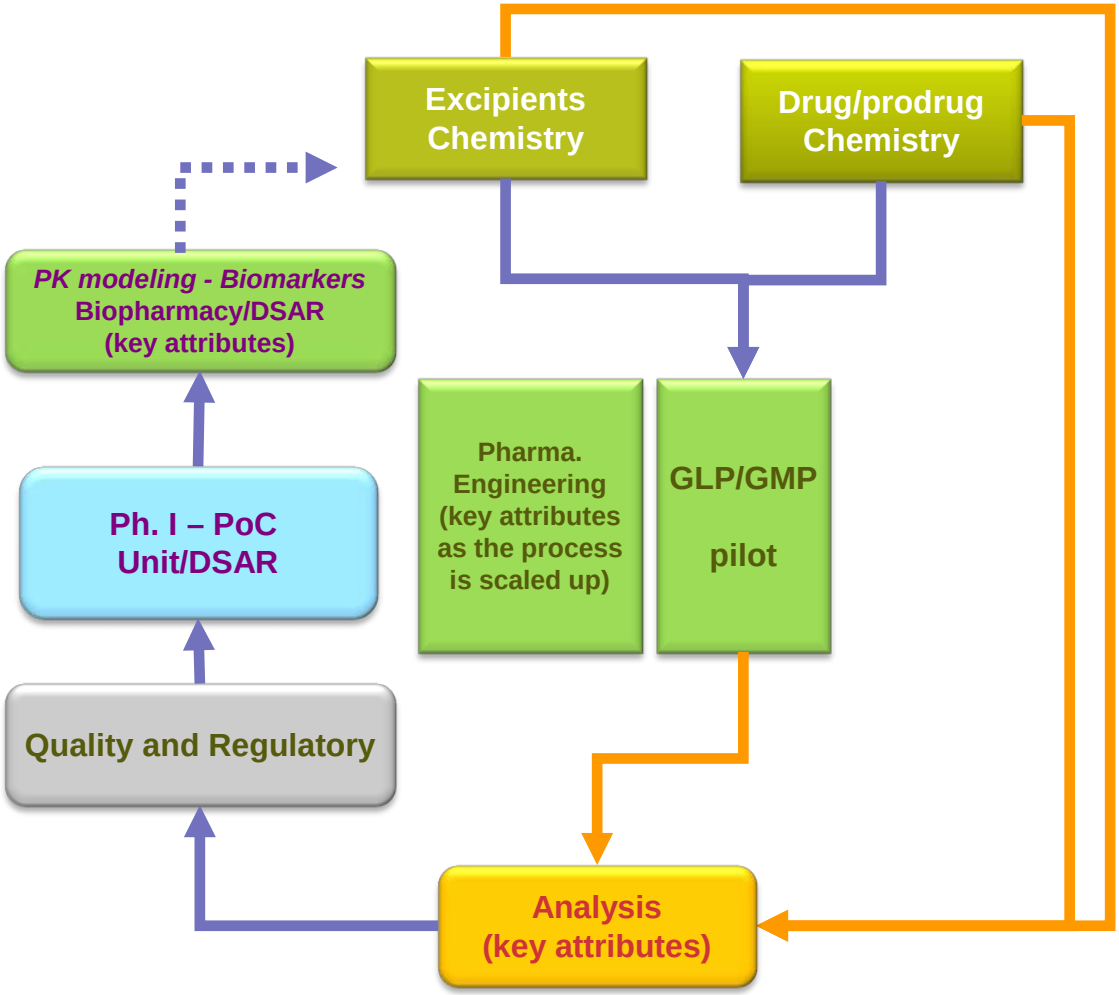
Drug Delivery Technologies and Innovation, Pharmaceutical Sciences, Sanofi Research and Development, Vitry-sur-Seine 94403, France

(*) : stability, release in simulated biological fluids.

Pharmacy – Science of drug/excipient(s) assembling

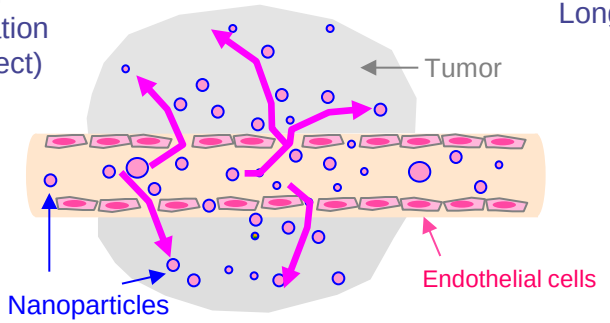
Clinical proof of concept (TRL 6-7)



Tumor accumulation – Drug Delivery concepts

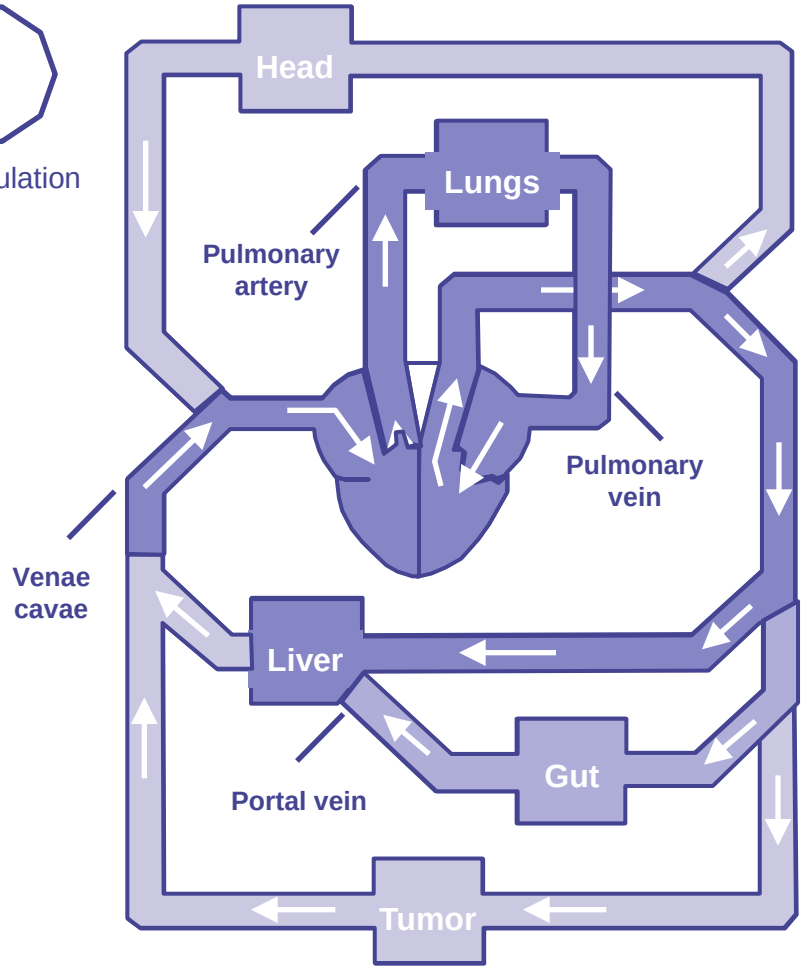
2

Tumor accumulation (EPR effect)



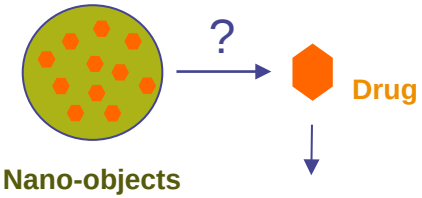
1

Long circulation



3

Encapsulation/release



Clearance

Advanced Drug Delivery Reviews 71 (2014) 34–57

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Drug/nano-carrier association

Drug delivery design for intravenous route with integrated physicochemistry, pharmacokinetics and pharmacodynamics: Illustration with the case of taxane therapeutics☆

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Drug Delivery Technologies and Innovation, Pharmaceutical Sciences Department, Sanofi Research and Development, 13 Quai Jules-Guesde, 94403 Vitry-sur-Seine, France

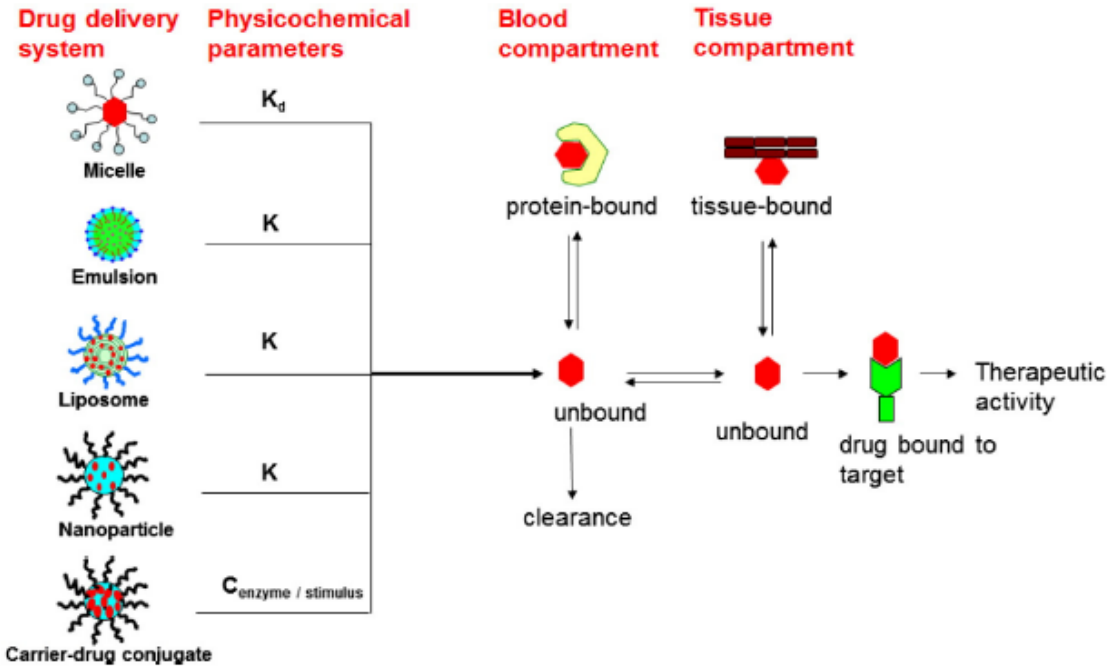

Fig. 6. Parameters controlling the drug release from the carrier after intravenous administration of different drug delivery systems. The drug release from the carrier is controlled by specific rate constants, which inturn influence the unbound drug concentration in the systemic compartment. Note: The size of the different drug carriers shown below may be different ranging from few nanometers to few hundreds of nanometers. K: partition coefficient, K_d: dissociation constant, $C_{enzyme/stimulus}$: enzyme/stimulus concentration.

Drug/nanoparticles association

BioMACROMOLECULES

Article

pubs.acs.org/Biomac

Y-Shaped mPEG-PLA Cabazitaxel Conjugates: Well-Controlled Synthesis by Organocatalytic Approach and Self-Assembly into Interface Drug-Loaded Core–Corona Nanoparticles

Fethi Bensaid,[†,‡] Olivier Thillaye du Boullay,[†,‡] Abderrahmane Amgoune,[†,‡] Christian Pradel,[†,‡] L. Harivardhan Reddy,[§] Eric Didier,[§] Serge Sablé,[§] Guillaume Louit,[§] Didier Bazile,[§] and Didier Bourissou*[,†,‡]

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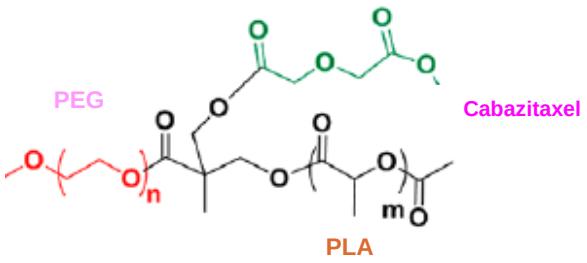
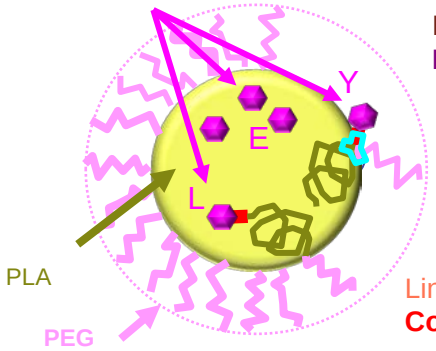
[§]Sanofi Research and Development, Lead Generation to Candidate Realization Platform, 13 Quai Jules Guesde, 94403 Vitry-sur-Seine, France



Y-shape chemistry

Université de Toulouse — Université Paul Sabatier TOULOUSE III

Cabazitaxel



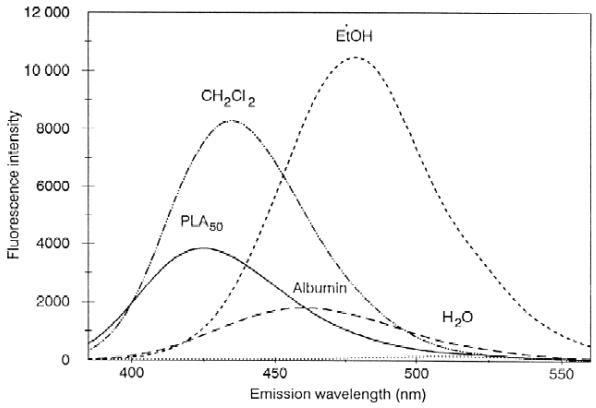
Encapsulation
Non covalent : release based on partition

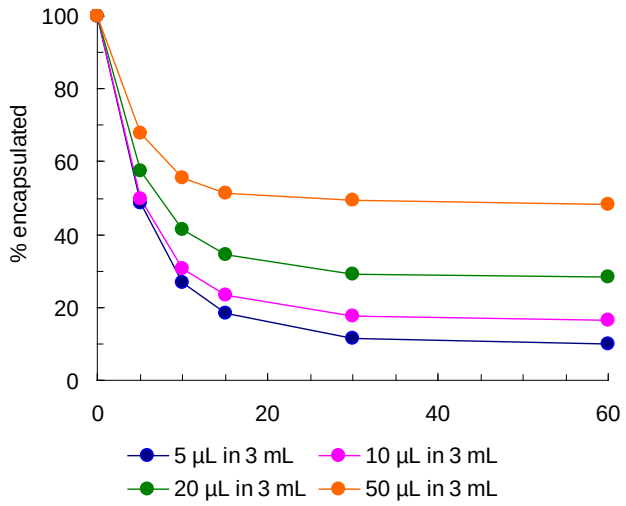
Y configuration (probed by NMR)
Covalent : release based on cleavage

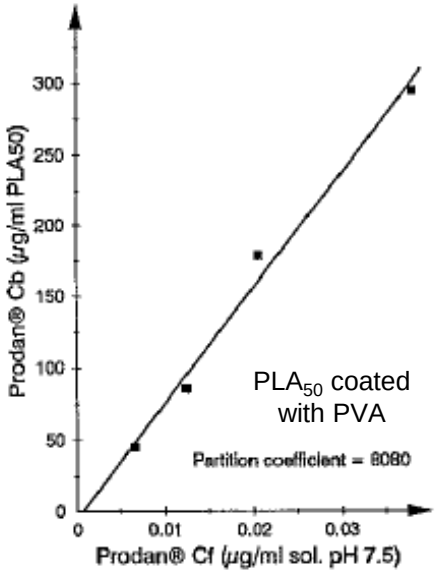
Linear configuration
Covalent : release based on cleavage

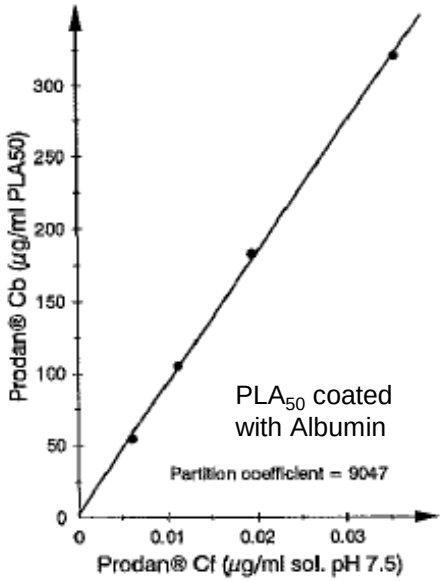
CMC NPP New Product Portfolio
External Innovation

Encapsulation of a fluorescent dye – Prodan®







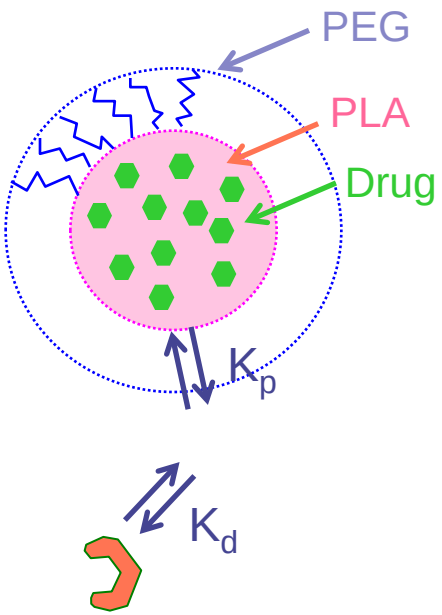


The release kinetics is independent of the dilution

Partition coefficient is independent of the coating agent

From Landry, F. et al. Journal of Controlled Release 44 (1997) 227–236

Long circulation and tumor accumulation



Plasma proteins

Need of a quality attribute for drug/particle interaction

➔ Partition coefficient

$$K_p = \frac{C_{encaps}^{drug}}{C_{free}^{drug}}$$

K_p high : risks of accumulation in non-desired compartments

K_p low : solution-like administration, no EPR effect

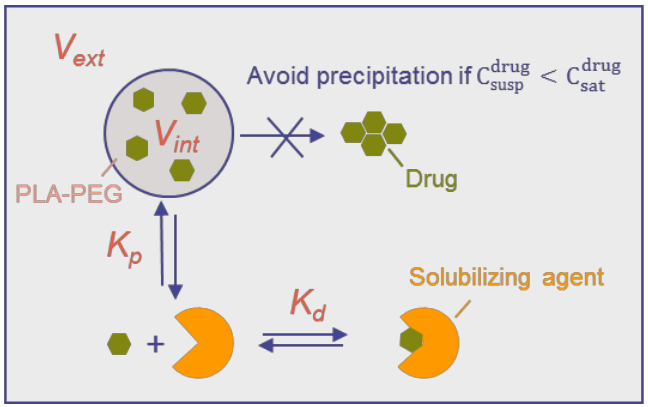
Nanoparticle/drug association – Partition - Principles

Pharm Res
DOI 10.1007/s11095-015-1696-0

RESEARCH PAPER

A method to Quantify the Affinity of Cabazitaxel for PLA-PEG Nanoparticles and Investigate the Influence of the Nano-Assembly Structure on the Drug/Particle Association

O. Diou[1] • S. Greco[1] • T. Beltran[1] • D. Lairez[2] • J.-R. Authelin[1] • D. Bazile[1]



- Thermodynamic constants: partition coefficient K_p and dissolution constant, K_d

$$K_p = \frac{C_{encaps}^{drug}}{C_{free}^{drug}}$$

Not measurable

$$K_d = \frac{C_{free}^{drug}\, C_{susp}^{solub}}{C_{bound}^{drug}}$$

Measured with S_{max}

- 2 steps indirect determination of K_p

$$K_p^{ap} = \frac{C_{encaps}^{drug}}{C_{diss}^{drug}}$$

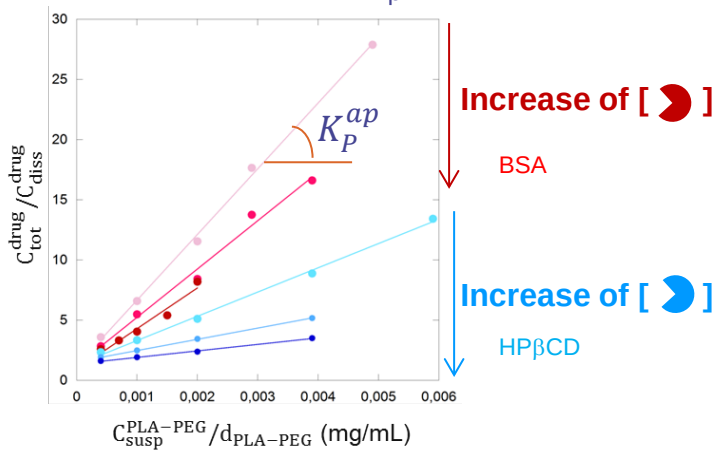
Separated by UC

$$K_p^{ap} = \frac{K_p K_d}{K_d + C_{susp}^{solub}}$$

Extrapolation to [ ]=0

Nanoparticle/drug association – Partition – Results

Determination of K_p^{ap}



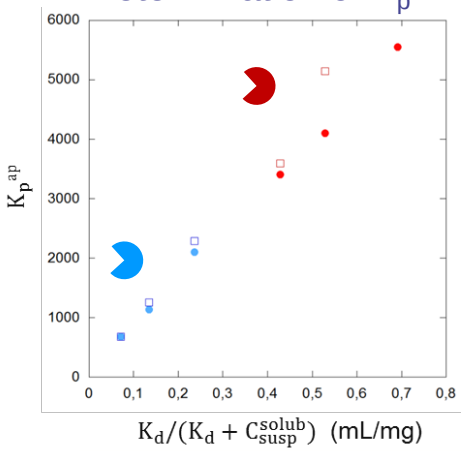
Increase of [ ]

BSA

Increase of [ ]

HPβCD

Determination of K_p



PLA-PEG$_{2000}$

Open squares : emulsion-evaporation
Filled circles : nanoprecipitation

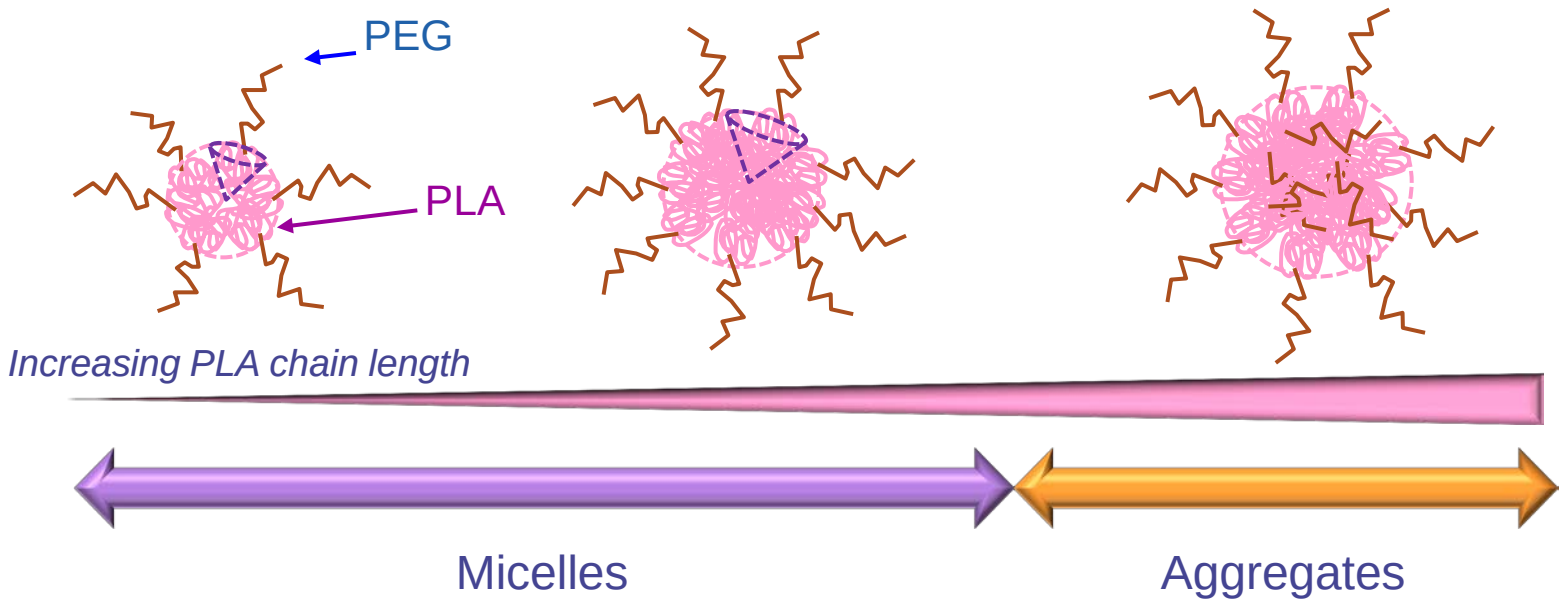
Polymer	PLA-PEG$_{2000}$	PLA-PEG$_{5000}$	PLA-PEG$_{2000}$	PLA-PEG$_{5000}$
Process	Emulsion-evaporation		Nanoprecipitation	
d_H (nm)	126	141	54	27
K_p	9253	8910	7997	13686
R^2	0,984	0,991	0,996	0,999

PLA chain length is 30 kd

K_p Significantly different

Validation of the experimental methodology by linearity (R^2>0,98) for 4 types of NP and 2 solubilizing agents

Topology of PLA-PEG nanoparticles



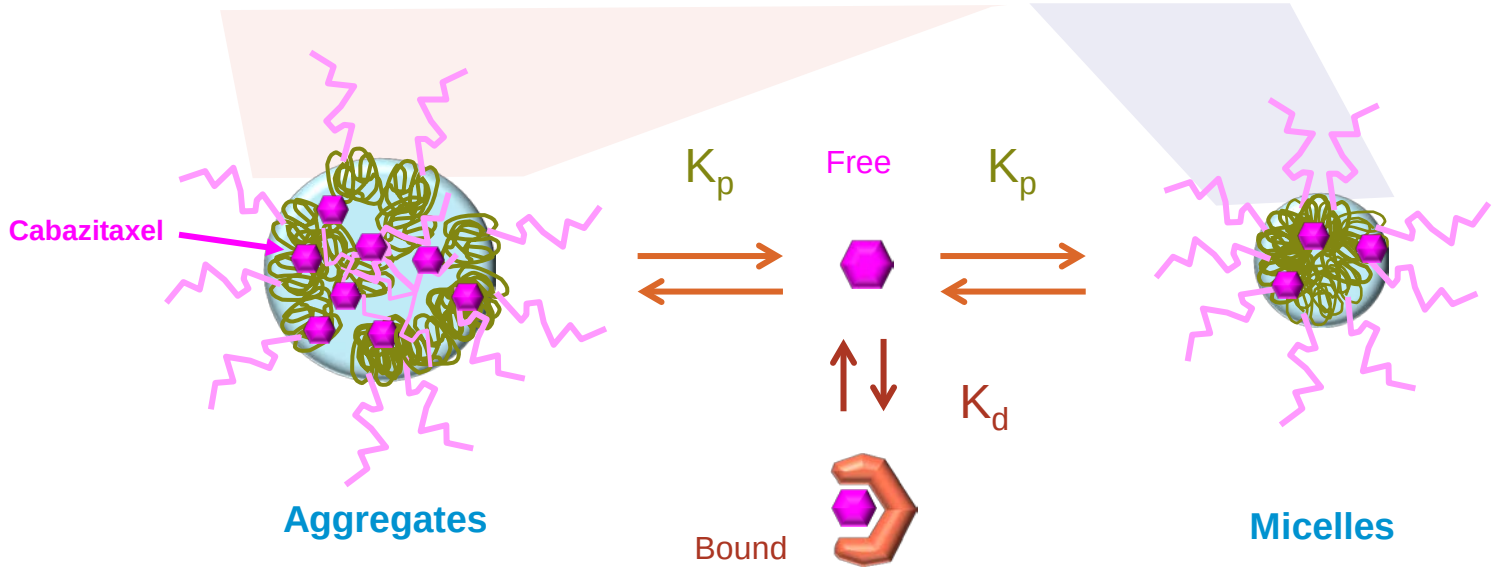
PLA-PEG nanoparticles topology (including PEG surface density) depends on:

- **PLA and PEG chain lengths,**
- **Nanoparticles manufacturing process (nanoprecipitation vs. emulsion-evaporation),**
- **Manufacturing conditions (concentration of polymer in the organic phase, type and concentration of surfactant in the aqueous phase).**

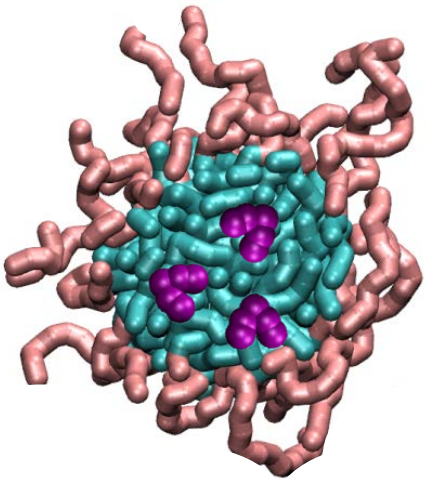
Correlation between the partition coefficient (Kp) and the structure of PLA-PEG nanoparticles

Polymer	$PLA\text{-}PEG_{2000}$	$PLA\text{-}PEG_{5000}$	$PLA\text{-}PEG_{2000}$	$PLA\text{-}PEG_{5000}$
Process	Emulsion-evaporation		Nanoprecipitation	
d_H (nm)	126	141	54	27
$V_{PLA\text{-}PEG}$ (nm^3/molec)	68	72	73	46
K_p	9253	8910	7997	13686

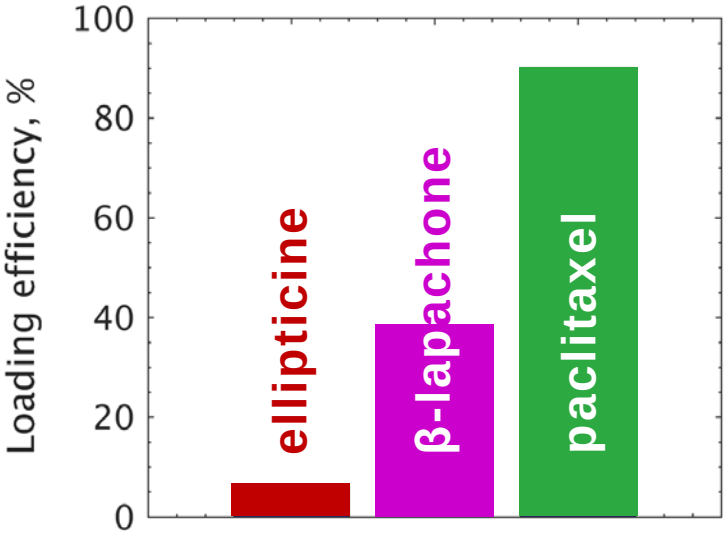
$K_p/V_{PLA\text{-}PEG}$ is constant



Molecular modeling of physicochemical & structural properties of PLA-PEG nanoparticles



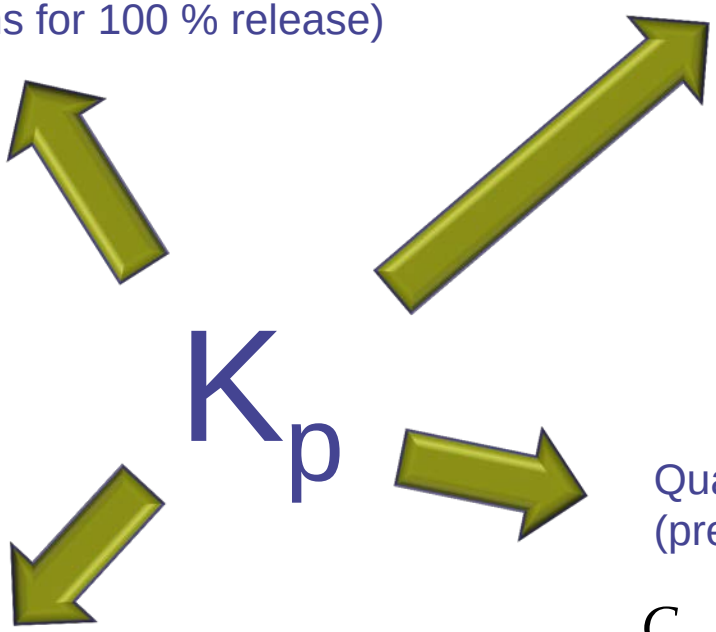
micelle



- **Does the novel drug suit a polymer-based nanoparticle formulation?**
- **Can molecular dynamics (MD) support experimental optimization?**
  - **rank drugs or polymers with respect to drug loading or release?**
  - **suggest polymer chain length / hydrophilic ratio resulting in nanoparticles with desired structural properties?**
- **Can we provide insights into events at the molecular level?**

Use of the partition coefficient

In vitro release tests design
(Conditions for 100 % release)



Maximal drug loading
(below crystalization conditions)

$$C_{free}{}^{drug} < \text{max. solubility in water}$$

Quantification of the drug in its various forms
(preclinical vs. clinical dose conditions)

$$C_{total} = C_{free} + C_{protein-bound} + C_{nano-encapsulated}$$

In silico determination of the aptness of drug to be encapsulated

$$\Rightarrow \quad C_{total} = C_{free} + \frac{C_{free}.C_{protein}}{K_d} + \frac{C_{free}.C_{polym}.K_p}{d_{polym}}$$

Conclusion

- **Wide range of application with multiple innovation drivers:**
  - **Material (lipids, polymers, metals, carbon, fullerenes, oxydes),**
  - **Nano-structure (spheres, capsules, rods),**
  - **Routing to organs (liver targeting, BBB crossing),**
  - **Intracellular delivery (DNA, mRNA, siRNA),**
  - **Theranostics,**
  - **Combination with radiation, heat, ultra-sounds.**
- **Sustained research efforts in pre-competitive research (European consortia, national and international workshops and initiatives) to fill methodological gaps.**
- **Technology Readiness Levels as a global framework for translation from bench to proof-of-concept in human.**
- **As opposed to (immediate release) standard formulations, in vitro release technique showing 100 % release is not enough to characterize the nano-formulation and manage the quality.**
- **Further improvements expected to manage the routing of the drug and anticipate the « off-target » effects (determination of free, plasma protein bound and encapsulated fractions).**

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