Master 2 Pharmacotechnie et Biopharmacie

Formes innovantes introduction (UE 3)

Simona Mura | September 12, 2024 |

Étapes biopharmaceutiques & pharmacocinétique

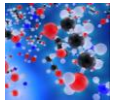
Devenir d'un principe actif dans l'organisme

(*) surtout

Libération L

Forme galénique (SA + excipients)

Dissolution D

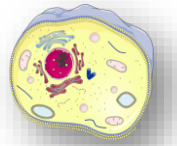


Site d'administration

A **Absorption**

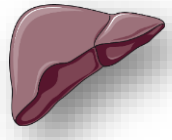
D **Distribution**

- Tissus
- Cellules
- Compartiments subcellulaires



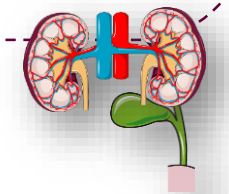
M **Métabolisation**

- Foie*



E **Elimination**

- Reins*
- Bile



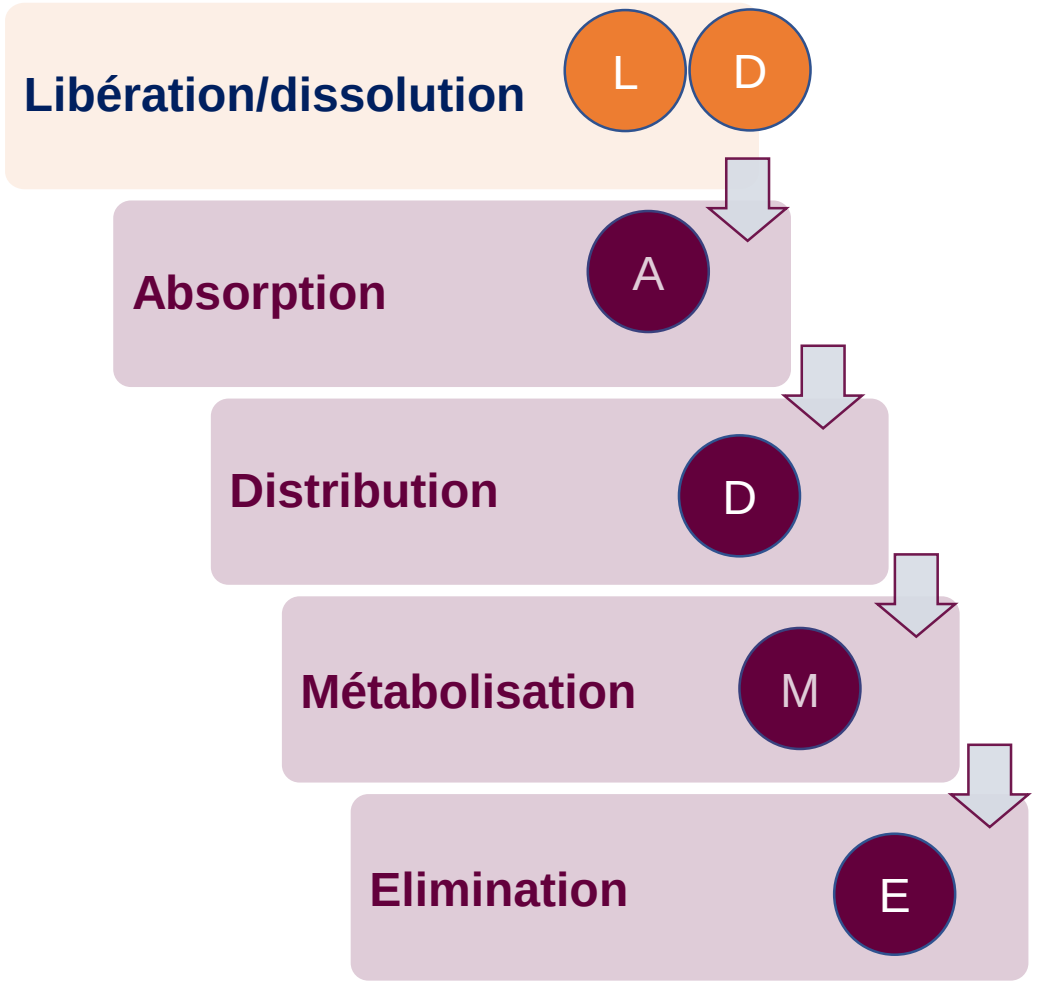
Aspects biopharmaceutiques

A D M E

Etapes Pharmacocinétiques

Étapes biopharmaceutiques & pharmacocinétique

Devenir d'un principe actif dans l'organisme



Étapes biopharmaceutiques & pharmacocinétique

Devenir d'un principe actif dans l'organisme

Libération/dissolution L D

Absorption A

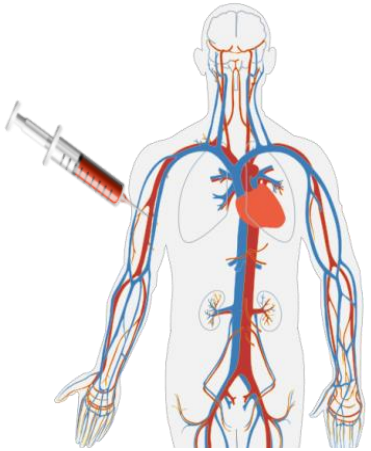
Distribution D

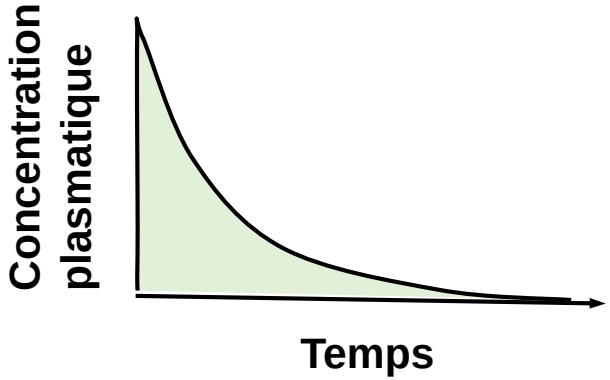
Métabolisation M

Elimination E

Administration par voie intraveineuse

La totalité de la dose administré atteint la circulation générale





Étapes biopharmaceutiques & pharmacocinétique

Devenir d'un principe actif dans l'organisme

Libération/dissolution — L D

Absorption — A

Distribution — D

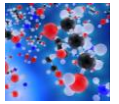
Métabolisation — M

Elimination — E

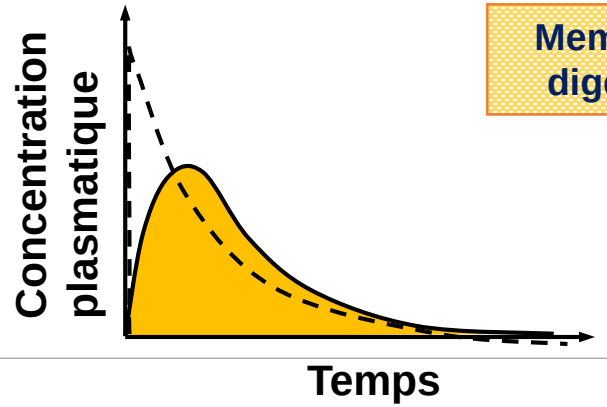
Autres voies d'administration

Libération

Dissolution

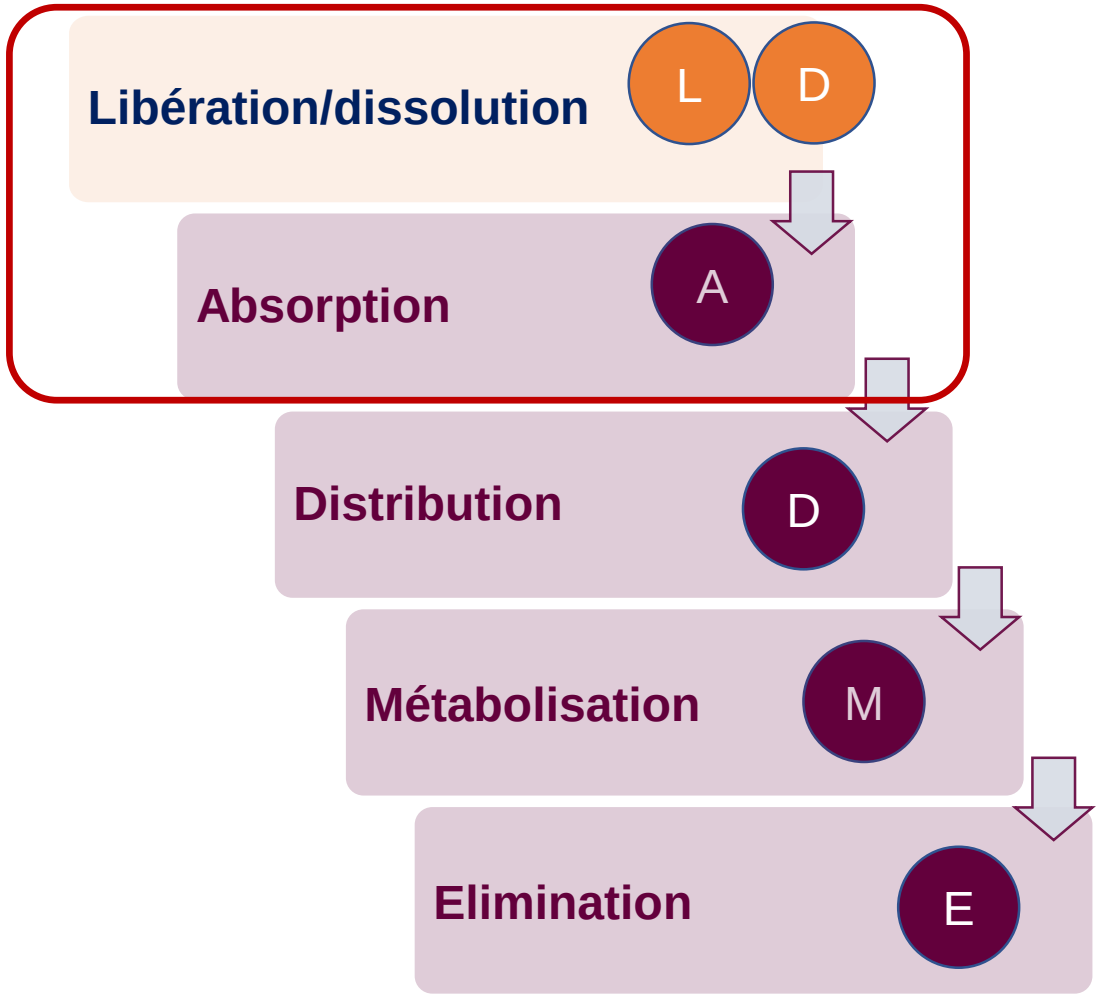


Membrane digestive



Étapes biopharmaceutiques & pharmacocinétique

améliorer l'administration et le devenir d'une SA ("delivery")



Améliorer la stabilité, la solubilité et/ou la dissolution de la substance active

Améliorer l'absorption de la substance active

Contrôler la mise à disposition de la SA

Étapes biopharmaceutiques & pharmacocinétique

améliorer l'administration et le devenir d'une SA ("delivery")

Libération/dissolution L D

Absorption A

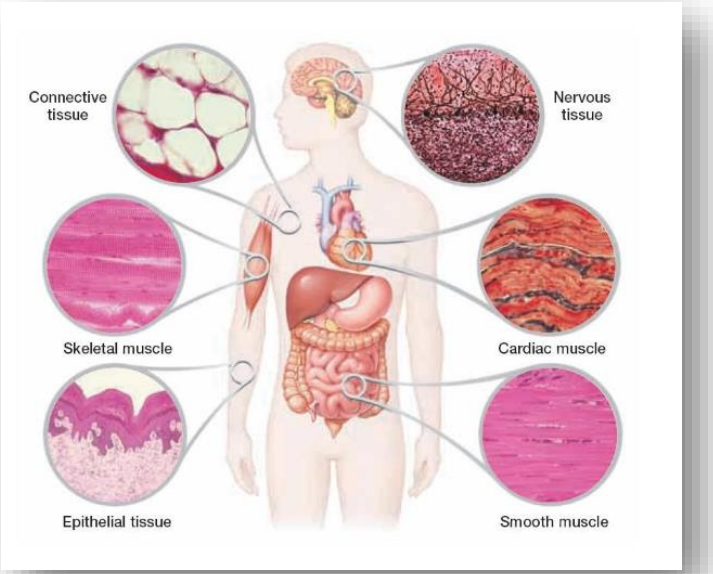
Distribution D

Métabolisation M

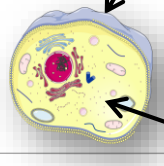
Elimination E

Vectoriser la SA pour le diriger vers la cible thérapeutique

SA & vecteur → *Tissus*



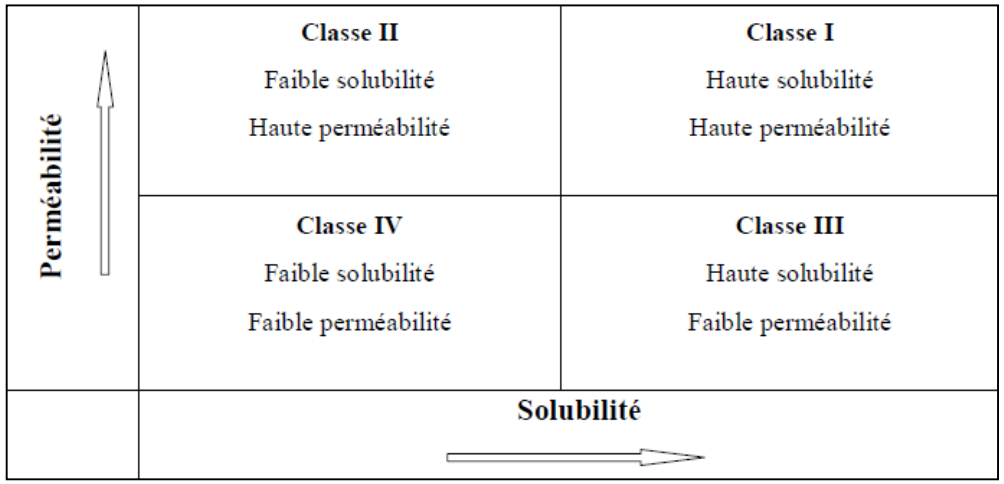
Cellules



Compartiments subcellulaires

Aspects biopharmaceutiques

Système de classification biopharmaceutique *Biopharmaceutics Classification System, BCS*



Haute solubilité :

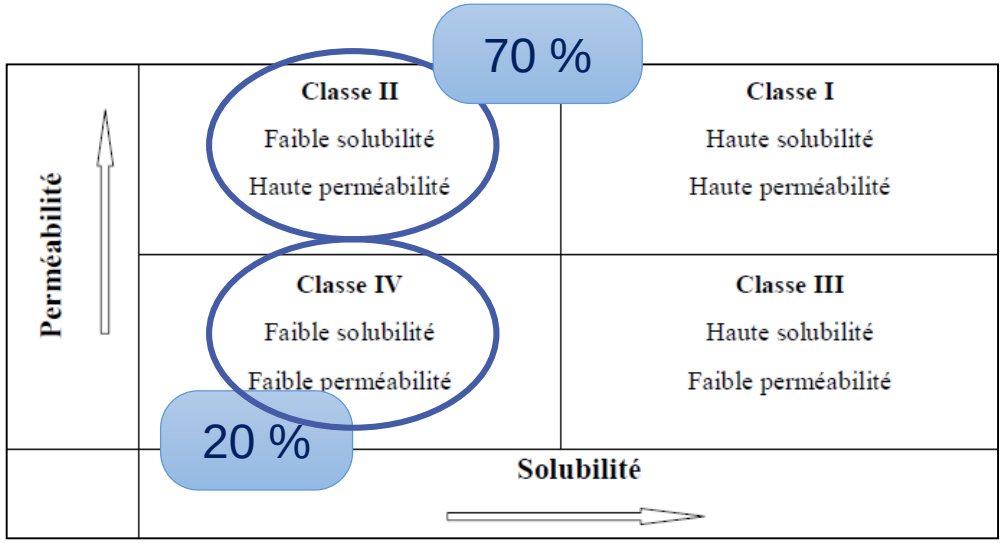
- la dose maximale prévue pour administration est soluble dans 250 mL d'un milieu aqueux avec un pH allant de 1 à 7.5 à 37 ± 1°C.

Haute perméabilité :

- plus de 90% de la dose de substance active administrée est absorbée

Aspects biopharmaceutiques

Système de classification biopharmaceutique *Biopharmaceutics Classification System, BCS*



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Aspects biopharmaceutiques

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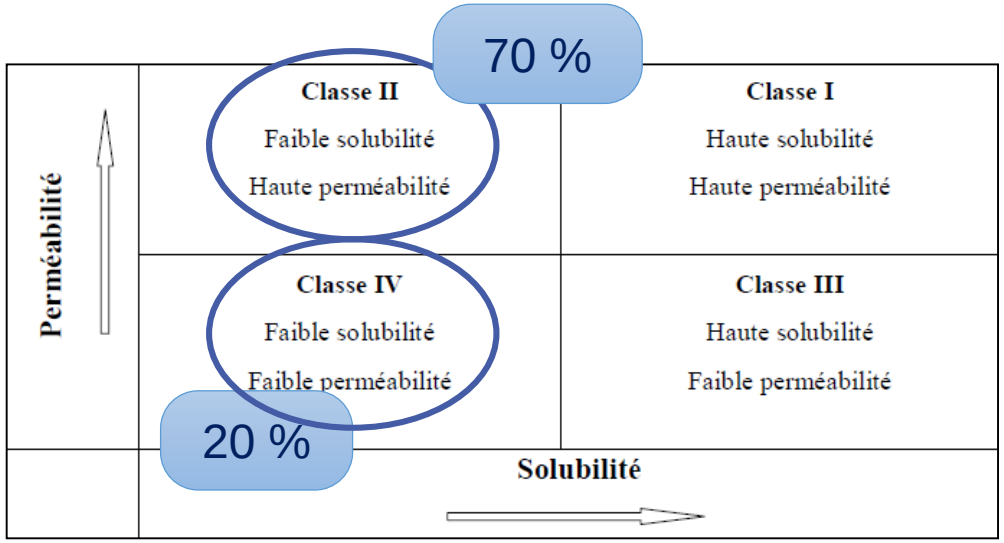

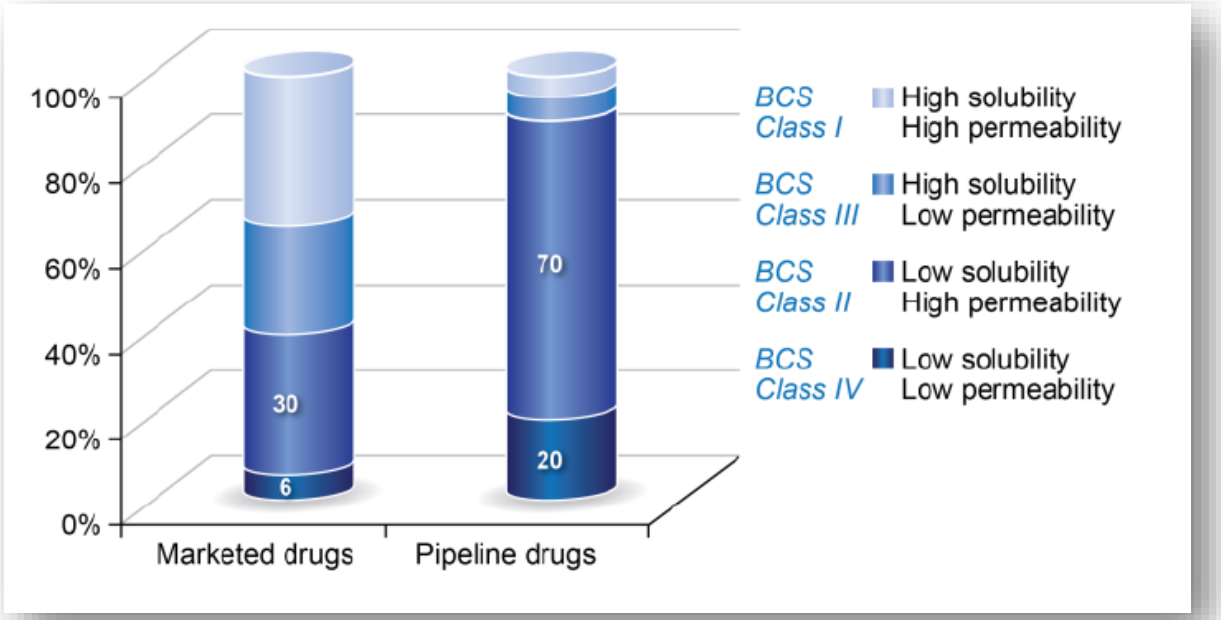

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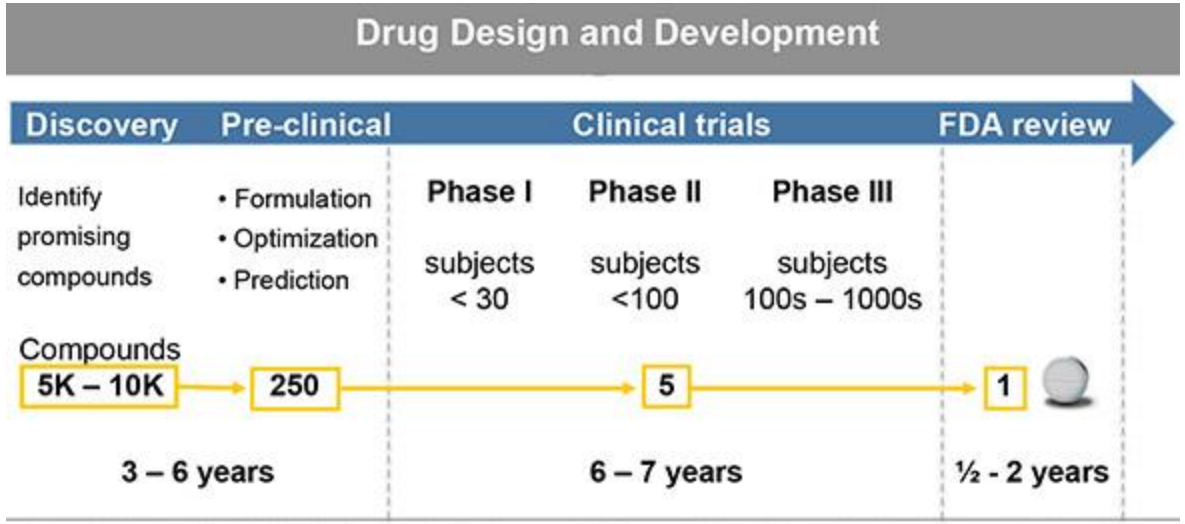
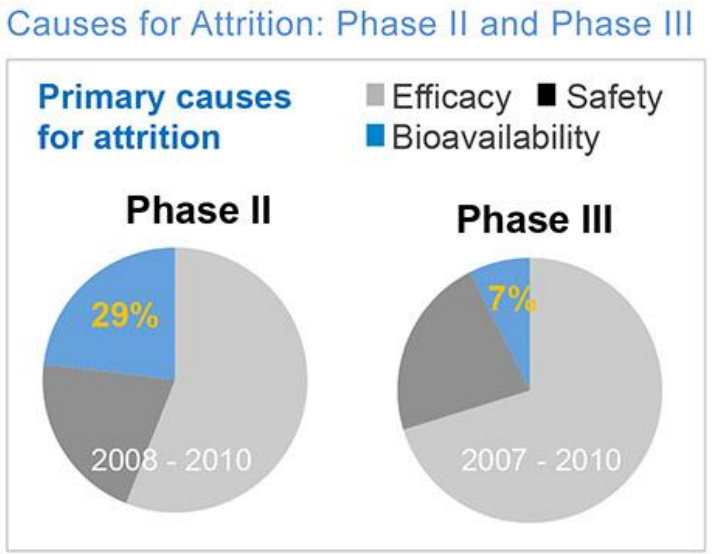
Adapted from: Lipp, R., The Innovator Pipeline: Bioavailability Challenges and Advanced Oral Drug Delivery Opportunities, American Pharmaceutical Review, 2013

Aspects biopharmaceutiques

Le développement du médicament





Parcours long et très réglementé qui a raison de nombreuses molécules candidates

- **Efficacité**
- **Toxicité**
- **Biodisponibilité**

Adapted from: Crew M, FORMULATION DEVELOPMENT – A Call for Collaboration to Meet the Bioavailability Challenge, Drug Development and delivery, 2013

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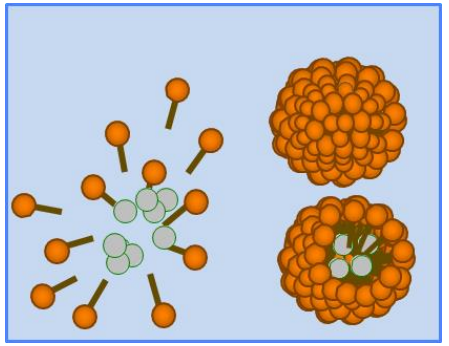
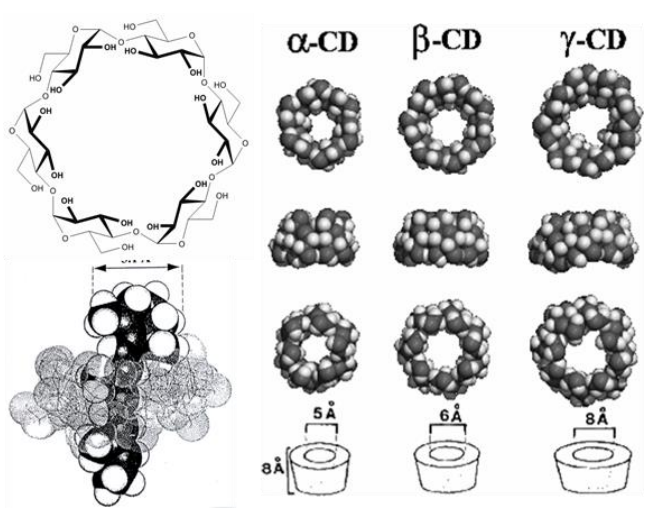
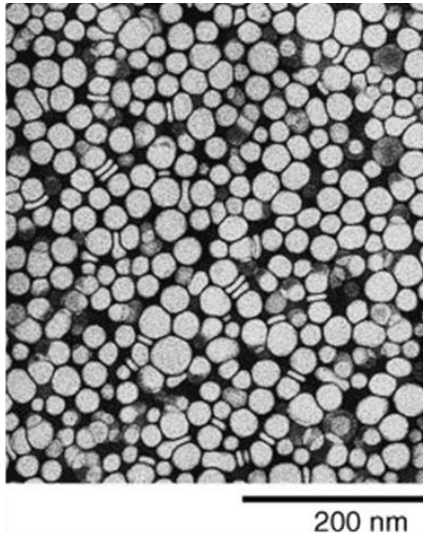
Stratégies de solubilisation

- Molécules cages: cyclodextrines
- Solubilisation micellaire
- Méthodes spécifiques pour les peptides, protéines et vaccins
- Emulsions







Adapted from: Crew M, FORMULATION DEVELOPMENT – A Call for Collaboration to Meet the Bioavailability Challenge, Drug Development and delivery, 2013

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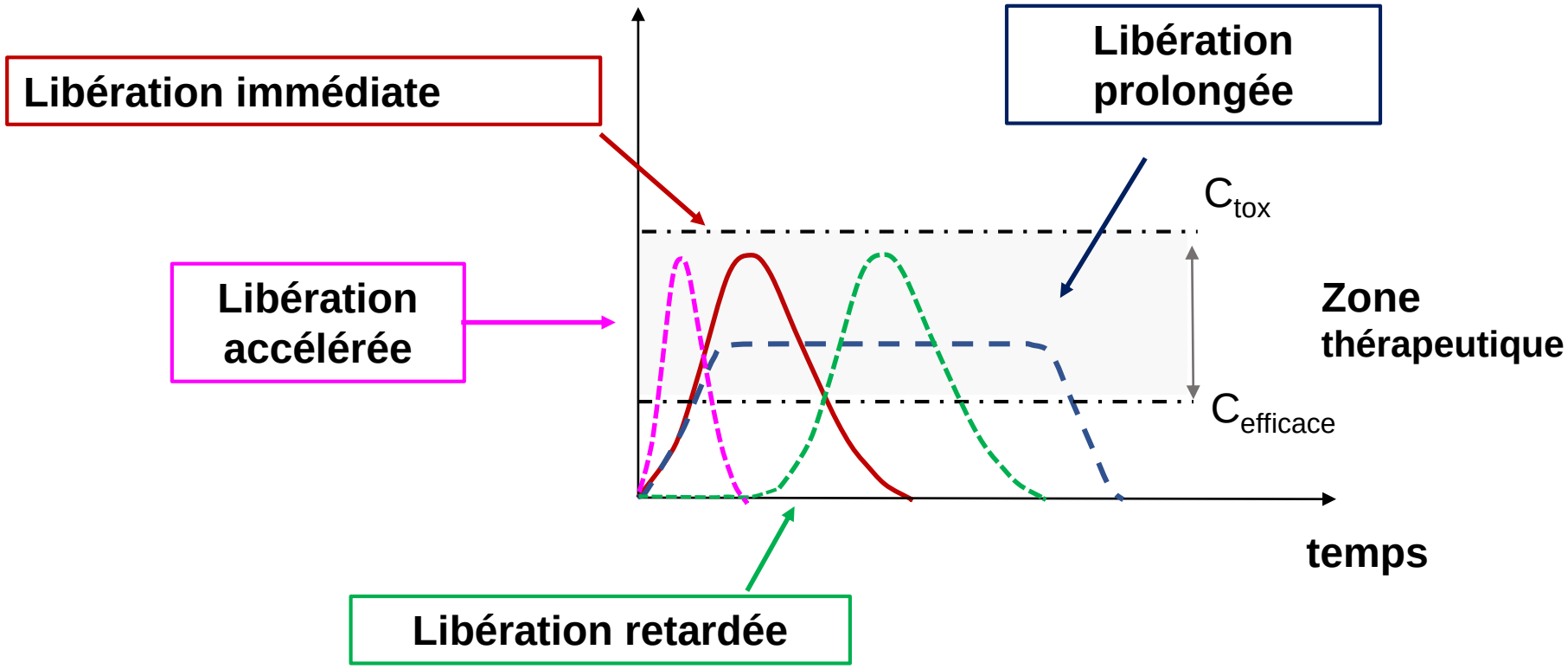
Modulation de la biodisponibilité



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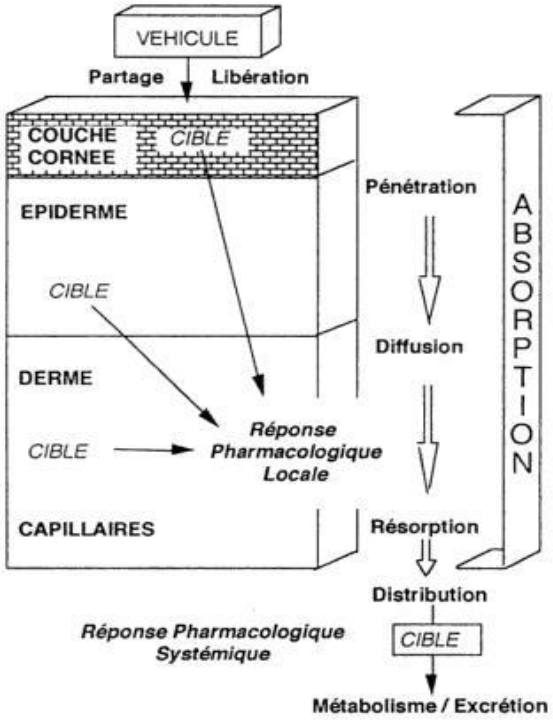
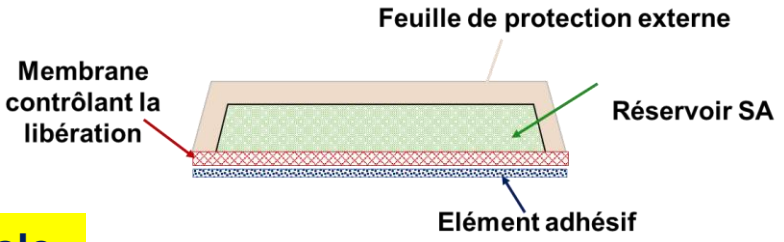
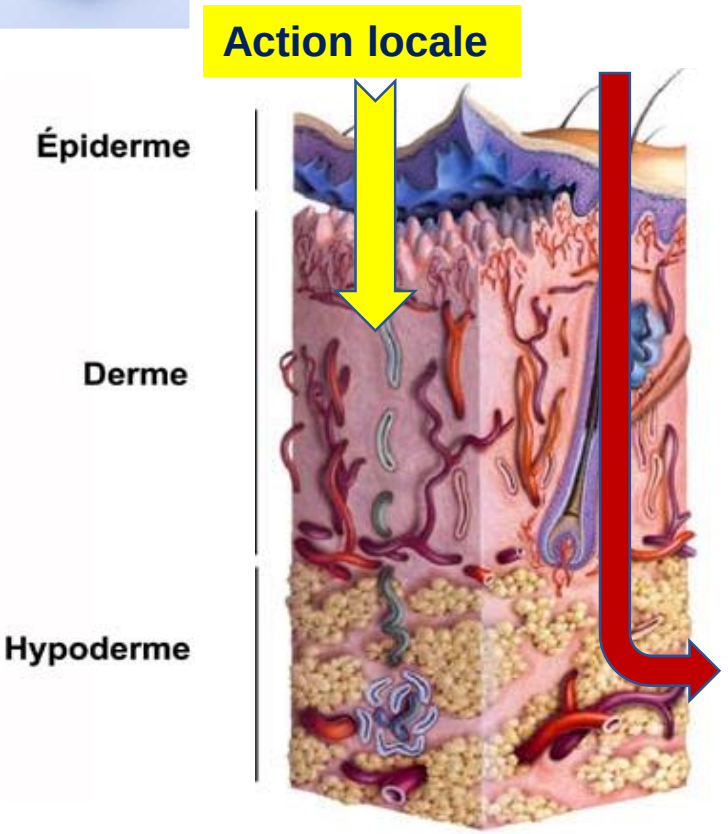
Modulation de l'absorption_Voie cutanée







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Modulation de la libération et/ou l'absorption_ Voie ophtalmique & Voie pulmonaire

REVIEWS Drug Discovery Today • Volume 24, Number 8 • August 2019

Teaser Recent findings regarding utilization of intravitreally injected nanoparticles for the retinal-targeted delivery of all types of therapeutics are summarized. The respective pharmacokinetic model for intravitreal nanoparticles was also developed.

Reviews • KEYNOTE REVIEW

Intravitreal nanoparticles for retinal delivery

Xiaonan Huang and Ying Chau

Department of Chemical and Biological Engineering, Hong Kong University of Science and Technology, Clearwater Bay, Kowloon, Hong Kong

Intravitreal injection is one of the major administration routes for the treatment of posterior ocular diseases. Intravitreal therapeutics usually suffer from unsatisfactory efficacy owing to fast clearance from the vitreous humour and insufficient distribution into the retina. Engineered nanoparticles have been applied for specific tissue targeting over the past decades. In this review, we summarize the most recent research utilizing intravitreal nanoparticles to deliver therapeutics to the retina. Herein, the achievement made in preclinical research and challenges remaining in the field are highlighted. Parameters including size, charge, stability and choice of modified ligand on intraocular distribution and transport are also systematically discussed based on a proposed pharmacokinetic model. We provide insights for rational design principles for intravitreal nanoparticles for targeted retinal delivery.

Introduction

The retina lies in the inner layer of the eye and is responsible for light transmission. The distortion and malfunction of the retina can lead to temporary or even irreversible vision loss, which makes the retina a drug target for multiple ocular diseases [1], such as glaucoma, age-related macular degeneration (AMD) and diabetic retinopathy (DR). Although eyedrops remain the most widely used administration route for various ocular conditions because of the ease of use for topical formulations, the efficiency of drug delivery to the retina via this route is poor because of anatomical and dynamic barriers, which have been extensively reviewed [2,3]. The most direct and relatively safe method for retinal delivery is by intravitreal injection. With limited space but adjacent to the retina, injection into the vitreous humour has been considered as the most efficient administration route with multiple advantages such as increased drug concentration in the neural retina and decreased systemic side-effects [4,5]. Despite the advantages, the fast depletion of drug in the vitreous usually necessitates frequent injections to maintain the concentration within the therapeutic window. Higher risks of cataract formation, endophthalmitis, retinal detachment and vitreous hemorrhage are associated with frequent intravitreal injections. Hence, drug delivery systems such as hydrogels and implants have been designed for

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Ms Xiaonan Huang is a PhD student in chemical and biological engineering at the Hong Kong University of Science and Technology. Her current research focuses on engineering nanoparticles with different parameters for specific targeting in retinal delivery. She received her BS and MS from Tianjin University.

Dr Ying Chau is Associate Professor of Chemical and Biological Engineering at the Hong Kong University of Science and Technology. Her current research interests include the design and translation of drug delivery approaches and biomaterials for ocular applications, and the self-assembly and cell interactions of nanostructures derived from polymers and biomolecules. She was a founding member of the biomedical engineering discipline in the Hong Kong Institutions of Engineers and is currently serving as a council member for the Hong Kong Biotechnology Organization. Dr Chau received her BS from Cornell University, MS from University of Pennsylvania and PhD in chemical engineering from Massachusetts Institute of Technology.

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nature biotechnology

Brief Communication https://doi.org/10.1038/s41587-023-01679-x

Combinatorial design of nanoparticles for pulmonary mRNA delivery and genome editing

Received: 21 July 2022

Accepted: 18 January 2023

Published online: 30 March 2023

Check for updates

Bowen Li[1,2,3,4,11], Rajith Singh Manan[1,2,11], Shun-Qing Liang[5,11], Akiva Gordon[1,2], Allen Jiang[1,2], Andrew Varley[3], Guangping Gao[5,6], Robert Langer[1,2,7,8,9], Wen Xue[5,10] ✉ & Daniel Anderson[1,2,7,8,9] ✉

The expanding applications of nonviral genomic medicines in the lung remain restricted by delivery challenges. Here, leveraging a high-throughput platform, we synthesize and screen a combinatorial library of biodegradable ionizable lipids to build inhalable delivery vehicles for messenger RNA and CRISPR–Cas9 gene editors. Lead lipid nanoparticles are amenable for repeated intratracheal dosing and could achieve efficient gene editing in lung epithelium, providing avenues for gene therapy of congenital lung diseases.

Congenital lung diseases such as surfactant protein deficiency disorders, cystic fibrosis (CF) and alpha-1 antitrypsin deficiency can lead to lifelong morbidity and mortality[1,2]. Although the genetic origins for these ailments have been identified, an effective treatment option remains elusive[3,4]. The intratracheal delivery of gene-editing tools, particularly CRISPR–Cas9, to the airway epithelium or other pulmonary cells presents a promising corrective approach to providing lifelong health and quality-of-life benefits for patients[5,6].

In vivo gene editing has been achieved using viral vectors such as an adeno-associated virus (AAV), but these stable DNA-based vectors lead to the long-term expression of Cas9 ribonuclease and single-guide RNA in cells[7]. While the extended exposure to editing machinery may favor gene correction rates, it can also lead to the accumulation of off-target genetic alterations[8,9]. Moreover, the immunogenicity of AAV capsids triggers neutralizing antibodies and T cell responses that limit repeated dosing of AAV-based treatments[10]; however, gene editing in the lung benefits from repeated dosing due to higher cell turnover rate[11]. Additionally, size limitations pose challenges for the integration of effective *Streptococcus pyogenes* CRISPR–Cas9 (SpCas9) constructs into AAVs[12]. These limitations can be overcome by nonviral, messenger RNA-based delivery platforms that enable transient expression and repeated dosing[13]. Lipid nanoparticles (LNPs) are the most clinically advanced nonviral vector, as seen with the widely accepted mRNA vaccine technologies developed by both Moderna and Pfizer/BioNTech, and show great promise in Cas9 hepatic gene-editing platforms[14–16]. However, an LNP-based Cas9 delivery system for efficient pulmonary gene modification has yet to be reported. Compared with the liver, the lung poses unique challenges for delivery due to its specialized cell types, mucus barrier and mucociliary clearance. Therefore, there remains a need for efficient approaches because airway epithelia remain poorly transduced by most viral and nonviral approaches[17].

Here we synthesized and screened a combinatorial library of biodegradable ionizable lipids to build nanoparticles for pulmonary mRNA delivery. Lead lipid formulations are amenable to multiple intratracheal dosing and can efficiently deliver Cre or Cas9 mRNA to mouse airway epithelium.

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News & views

Drug delivery https://doi.org/10.1038/s41563-023-01491-7

Inhalable mRNA nanoparticles

Ronnie H. Fang & Liangfang Zhang

Check for updates

A large-scale screening identifies an inhalable polymer nanoparticle formulation that safely and effectively delivers therapeutic mRNA molecules to the lungs of several animal species.

The COVID-19 pandemic has highlighted the potential of mRNA-based medicine for vaccine applications[1]. In principle, any type of protein can be expressed using mRNA technology, thus making it broadly applicable for the prevention and treatment of many diseases[2]. Despite their immense promise, mRNA molecules are fragile, and it is difficult for them to get inside cells, where they can engage with the cellular machinery that is responsible for converting their encoded information into proteins. To overcome these challenges, mRNA molecules can be encapsulated in nanoparticle carriers that offer protection from degradation by enzymes while enhancing cellular entry[3]. Current mRNA-based nanovaccines being used in the clinic to battle severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are administered intramuscularly; however, they are ineffective when delivered to the lungs via inhalation, which is a highly desirable route of administration due to its relative simplicity and potential for improved patient compliance. Now, writing in *Nature Materials*, Rotolo and co-authors[4] report on mRNA polymeric nanoparticles that can be safely delivered to the lungs of animals of various species using a nebulizer to elevate the local production of therapeutic proteins (Fig. 1).

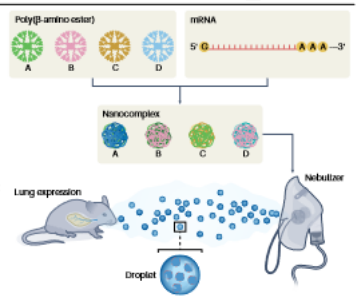

Fig. 1 | Screening of mRNA nanocomplexes for protein expression in the lungs. An mRNA payload is combined with a library of poly(β-amino esters) to form mRNA nanocomplexes. The activity of each nanocomplex is then screened in vivo by delivering it to the lungs via nebulization. Figure adapted with permission from ref. 4, Springer Nature Ltd.

To create the mRNA nanoformulation, a library of 166 different polymers based on a previously reported hyperbranched poly(β-amino ester) was constructed. Each of the polymers containing various modifications was combined with mRNA encoding for a protein construct. The resulting nanocomplexes were then evaluated for their ability to transfect the lungs of mice. To facilitate the in vivo screening process, the authors employed a nebulizer setup with a low dead-volume that reduced the amount of sample required for each experiment. From the initial screen, five promising formulations were identified based on their efficiency in delivering mRNA to the lungs, and finally a single lead polymer candidate containing a dithiol group, identified as P76, was selected.

Using the P76 polymer, mRNA of increasing sizes encoding for a variety of proteins was successfully formulated and delivered to the lungs of mice for protein expression. These data provided a strong indication that the platform could be employed for 'plug-and-play' mRNA delivery, where the mRNA payload can be easily swapped for another one depending on the desired application. Next, a comprehensive set of safety studies was performed, demonstrating that the nanoparticle formulation does not induce any toxicity when delivered to the lungs. Further validation studies in hamsters, ferrets, cows and monkeys confirmed the efficiency of this polymer formulation in delivering mRNA to the lungs of different animals. mRNA nanocomplexes produced using the P76 polymer were well tolerated in all animal species, while also improving in vivo protein production compared with formulations made using a previously reported poly(β-amino ester) polymer.

To evaluate the performance of the platform in a clinically relevant disease setting, a hamster model of SARS-CoV-2 infection was employed. As a treatment, the animals were administered a P76 nanocomplex loaded with RNA molecules for producing a Cas13a-based CRISPR complex against the SARS-CoV-2 nucleocapsid protein (an important structural component of the virus). Treatment with the nanoformulation protected the hamsters against the ill effects of SARS-CoV-2 infection, resulting in healthy weight gains over time in comparison to untreated animals and those that were treated with the same RNA but complexed with a control poly(β-amino ester) polymer. On a per milligram basis, the RNA-based treatment also outperformed the systemic administration of a virus-neutralizing antibody, which the authors employed as a gold-standard control treatment.

The work of Rotolo and co-authors highlights the advantages of performing large screens to identify promising nanomaterials that can be used for different biomedical applications. In this case, a highly functional polymer for effective mRNA delivery to the lungs was successfully identified, and this could have important implications for the treatment of various lung-related pathologies. For example, cystic fibrosis is characterized by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene[5], and thus an mRNA-based

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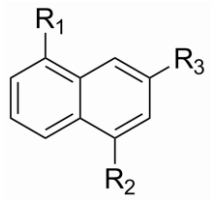
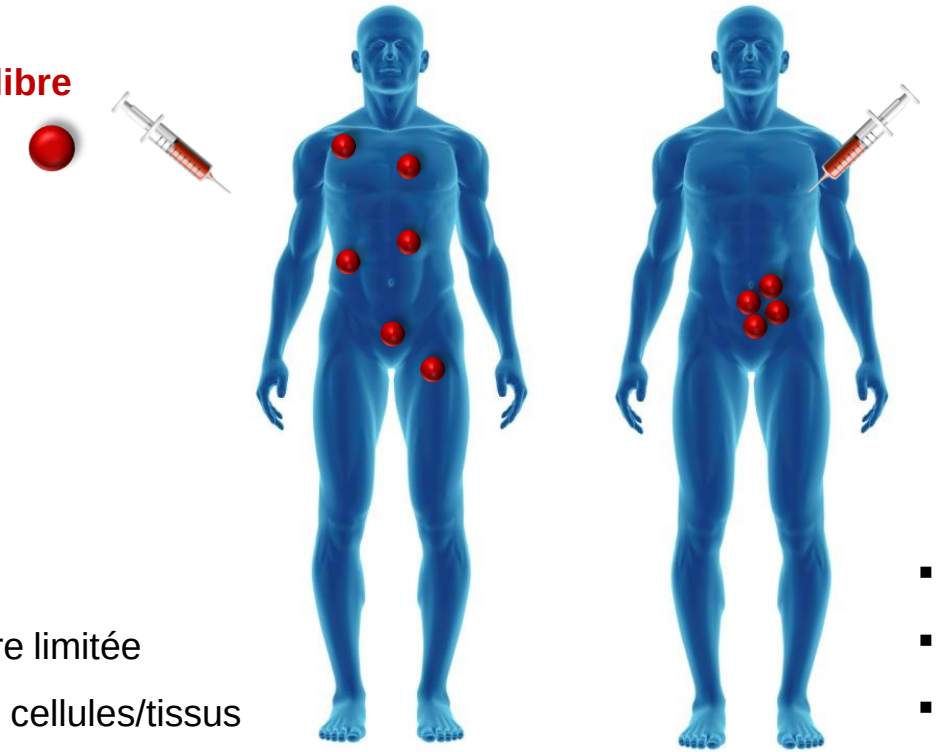
Modifier la distribution_vectorisation

Chimiothérapie traditionnelle

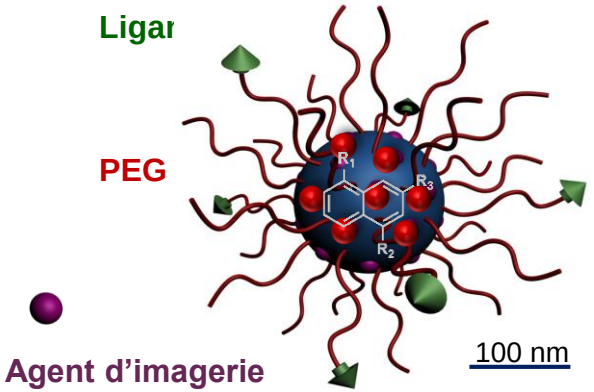
Molécule en forme libre





- Instabilité/métabolisation
- Accumulation intracellulaire limitée
- Manque de spécificité des cellules/tissus
- Induction de phénomènes de résistance

Nanomédicament

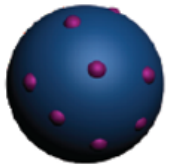


Nanoparticule

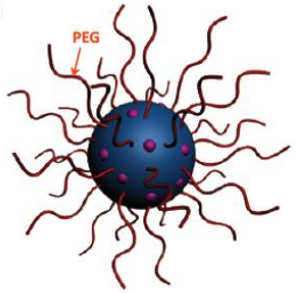
- Protection contre la dégradation
- Augmenter la pénétration intracellulaire
- Ciblage des cellules/tissus
- Vaincre les résistances
- Sensibilité accrue/détection plus rapide des maladies

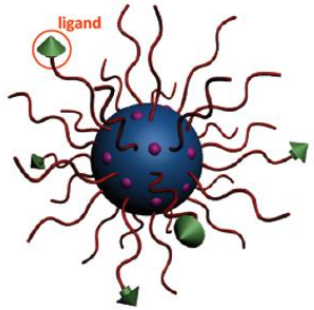
Galénique innovante

Modifier la distribution_vectorisation



Molécule en forme libre





1ere génération

2ème génération

Systèmes « furtifs »

3ème génération

Systèmes « furtifs » ET ciblés

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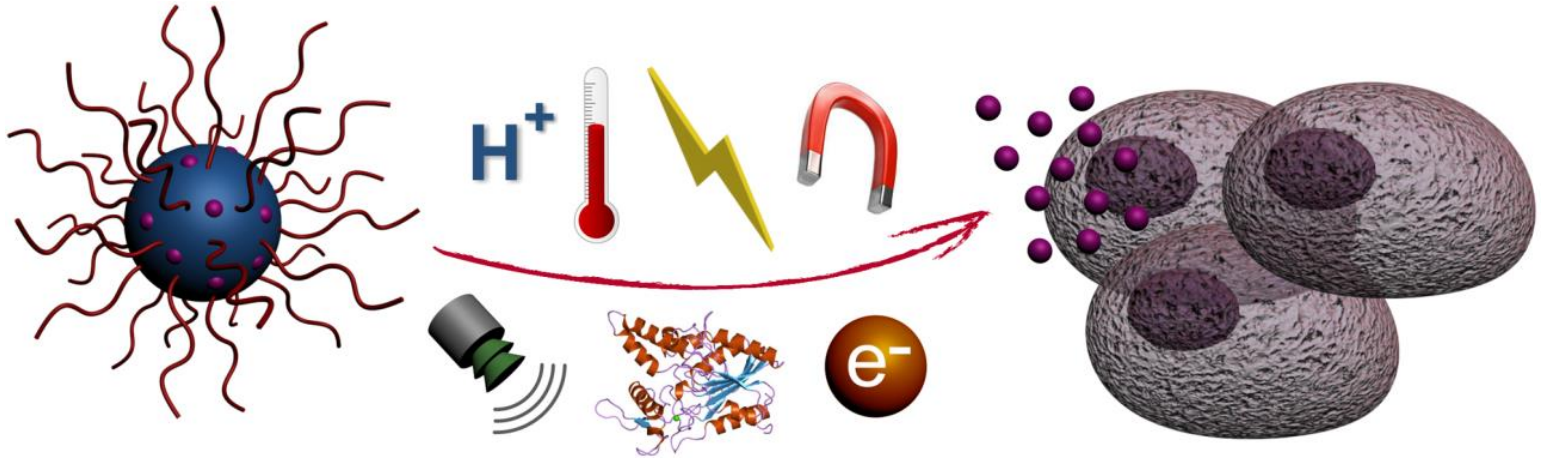
Modifier la distribution_vectorisation_sensible aux stimuli



Endogenous stimuli

- pH
- État d'oxydoréduction (concentrations de glutathion)
- Activité enzymatique

Exogenous stimuli

- Champ magnétique/électrique
- Lumière
- Ultrasons
- Température

S. Mura, J. Nicolas, P. Couvreur, , Nature Materials 2013, 12, 991

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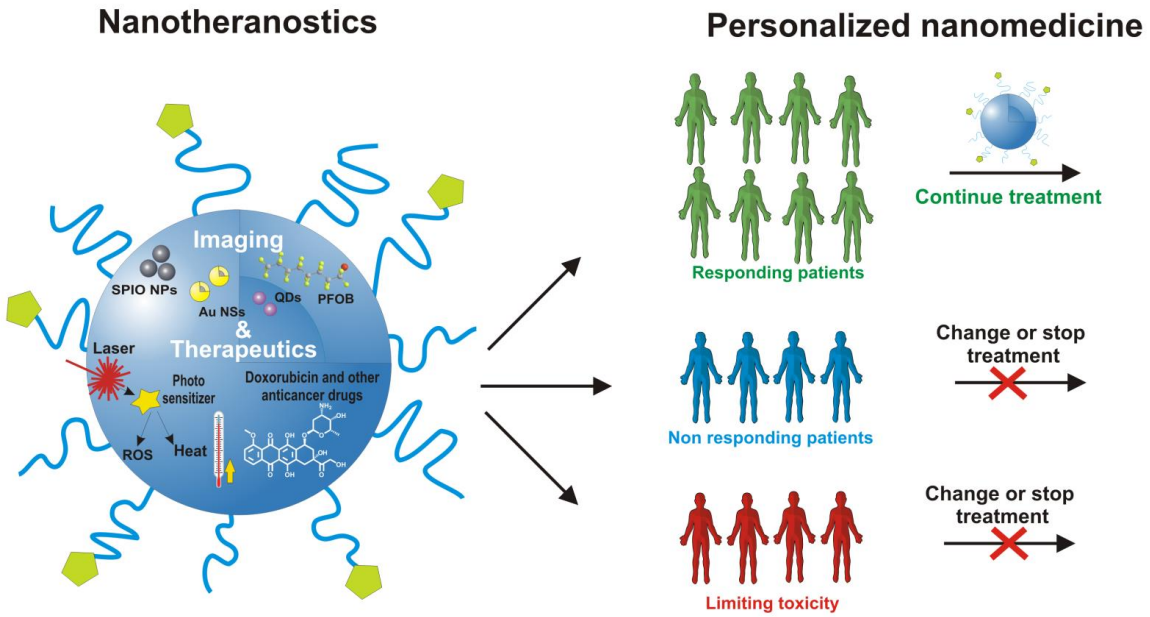
Modifier la distribution_vectorisation_ médecine de précision



Traitements optimisés et individualisés

- Suivi longitudinal non invasif
- Évaluation de la progression de la maladie
- Évaluation de l'efficacité des traitements à un stade précoce

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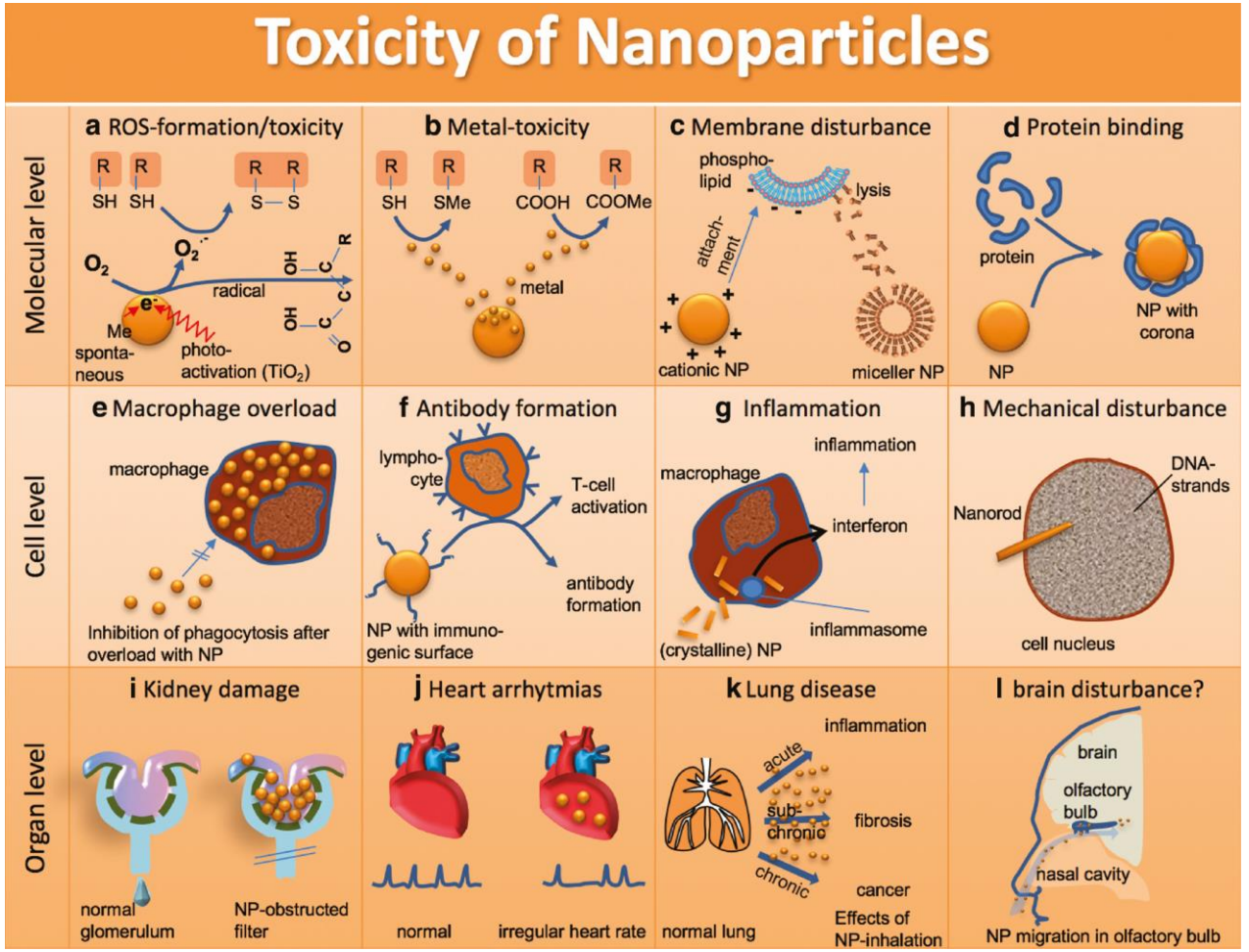
Nanotoxicologie



Pure Appl. Chem. 2018; 90(8): 1325–1356

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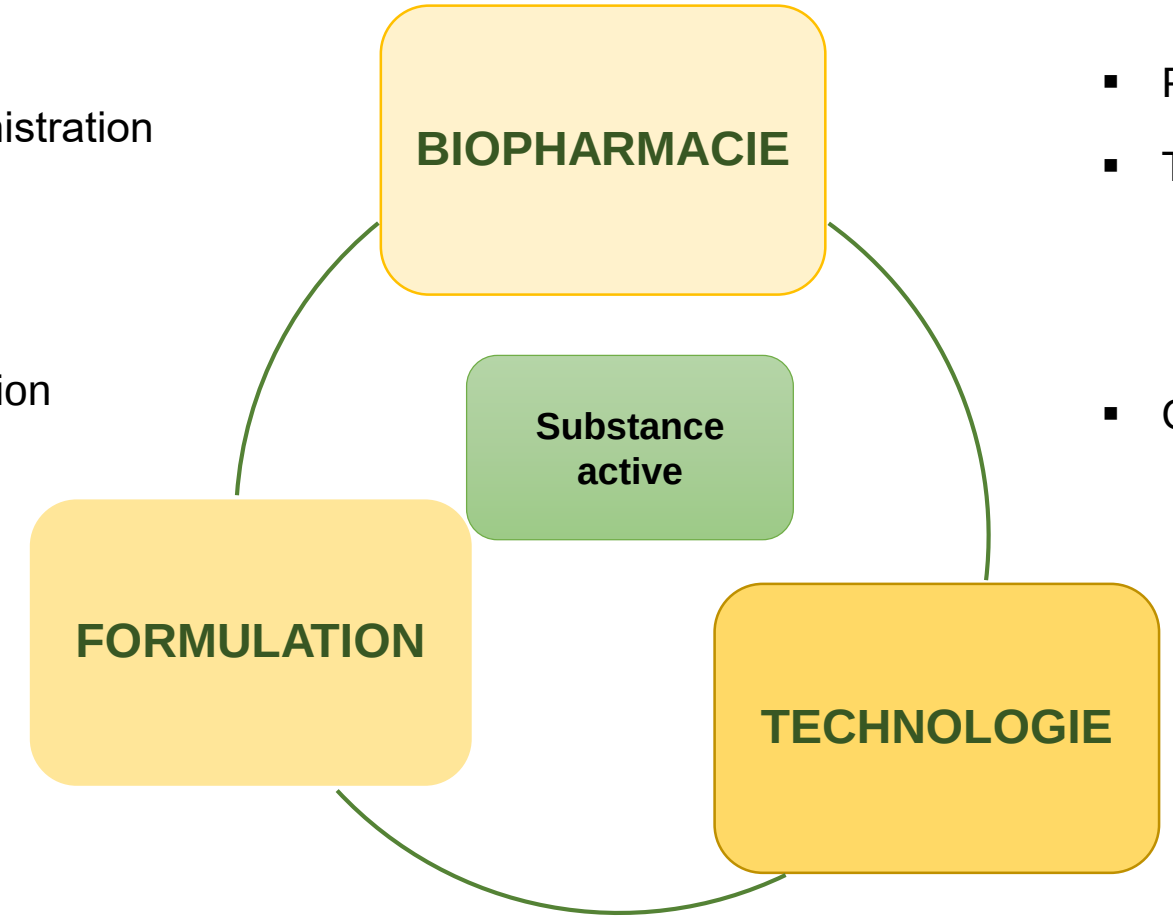
- Voie d’administration
- Pré-formulation
- Propriétés physico-chimiques



- Pharmacocinétique
- Toxicologie
- Génie des Procédés
- Plans d’expériences

Q&A