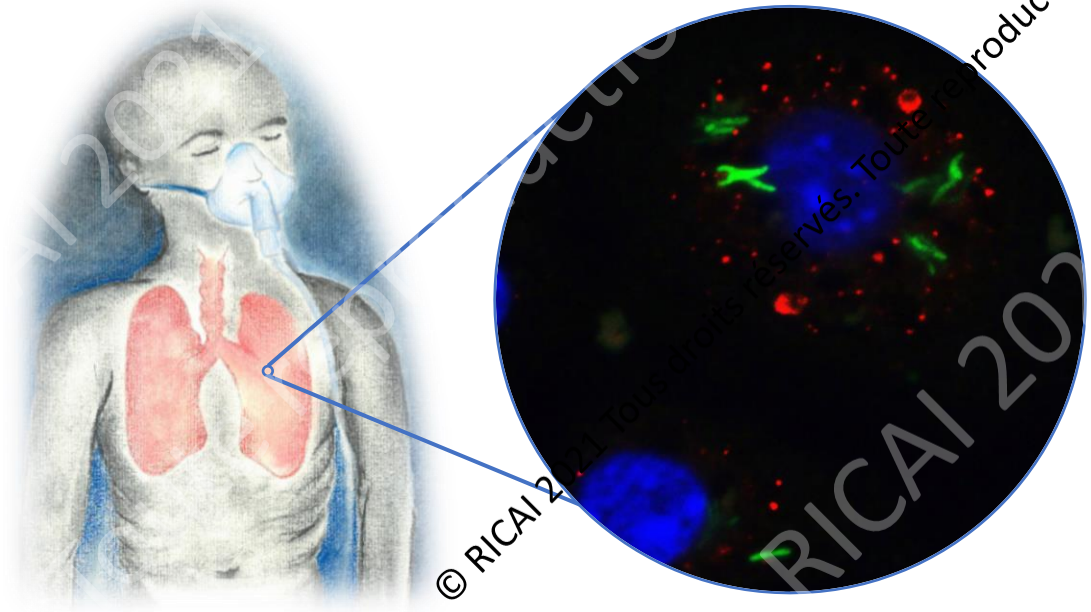
41e RÉUNION INTERDISCIPLINAIRE DE CHIMIOTHÉRAPIE ANTI-INFECTIEUSE
LUNDI 13 & MARDI 14 DÉCEMBRE 2021
PALAIS DES CONGRÈS • PARIS

The use of nanomaterials to improve antibiotic therapies : the case of polymeric cyclodextrins against tuberculosis



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Infectious diseases and antimicrobial resistance

About 8 million deaths each year

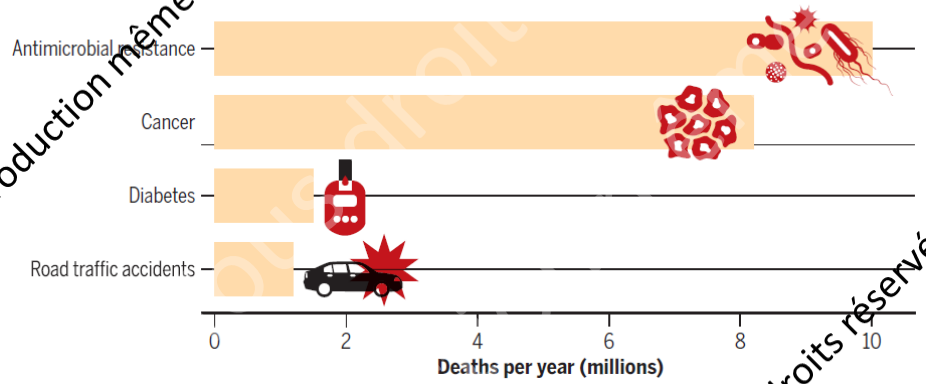
Top antibiotic-resistant threats in the United States

Urgent threats
- *Clostridioides difficile*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae*

Serious threats
- Multidrug-resistant *Acinetobacter*
- Drug-resistant *Campylobacter*
- Fluconazole-resistant *Candida*
- ESBL-producing Enterobacteriaceae
- Vancomycin-resistant *Enterococcus* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant nontyphoidal *Salmonella*
- Drug-resistant *Salmonella* serotype Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant Tuberculosis

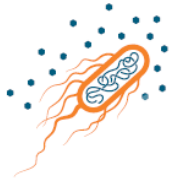
Concerning threats
- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Erythromycin-resistant group A *Streptococcus*
- Clindamycin-resistant group B *Streptococcus*

Annual global mortality projected for 2050



Ordonez, Sci Transl Med. 2019

Antibiotic treatment failures



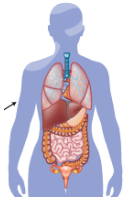
Drug-resistance

Compromised immune system

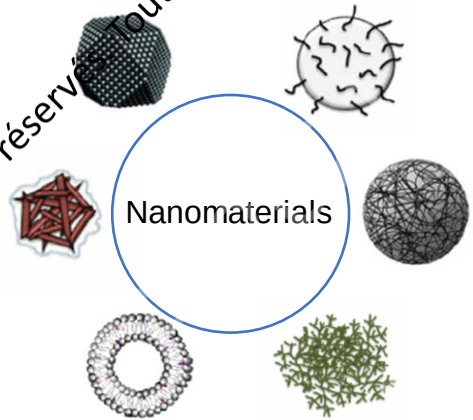
prolonged antibiotic treatments

Lack of new drugs

Drug toxicity



Bioavailability issue

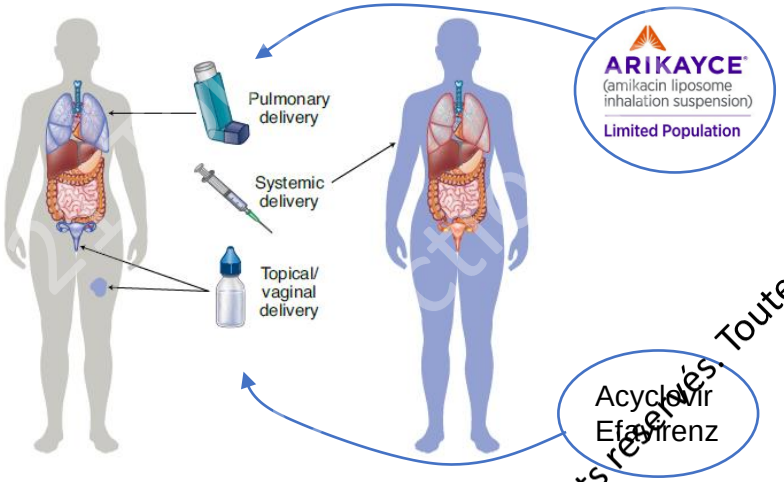


Liposomes
Polymeric nanoparticles
Nanocrystals
Nanotubes
Metallic nanoparticles

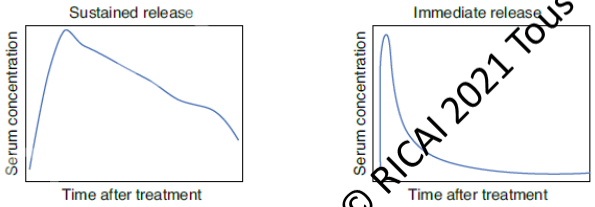
Nanomaterials to improve drug biodisponiblity

➡ To target the site of infection

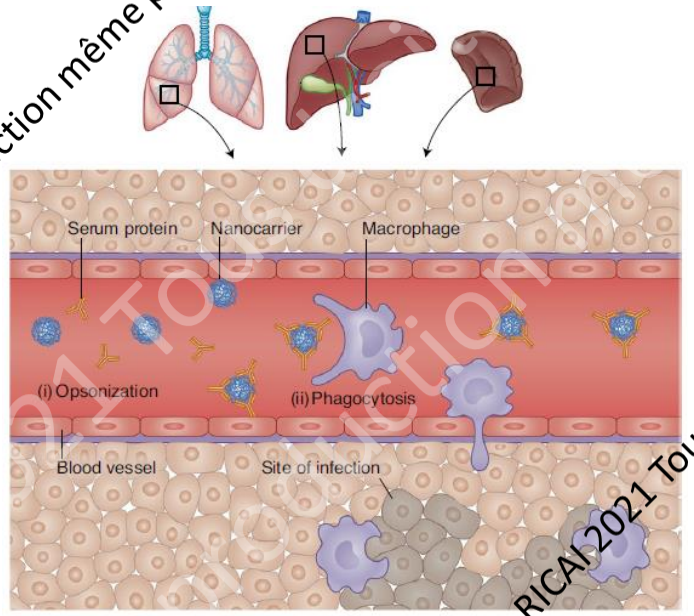
Local administration



Toxicity/Solubility/Drug-release



Nanocarriers opsonization



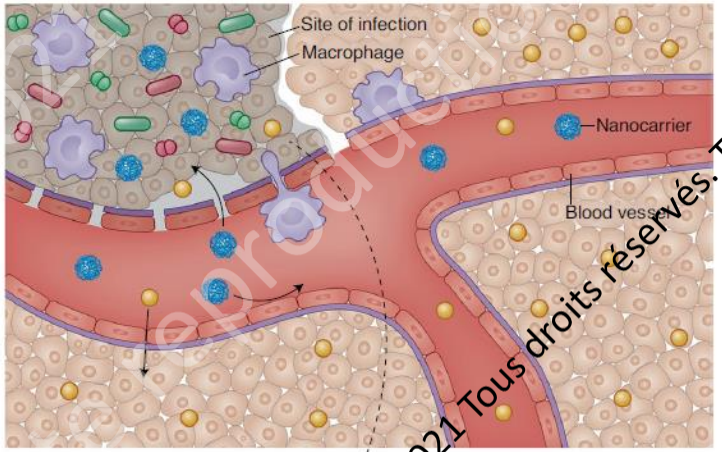
Serum proteins adsorption → Phagocytosis → Tissue invasion

Kirtane, Nat Nanotechnol. 2021

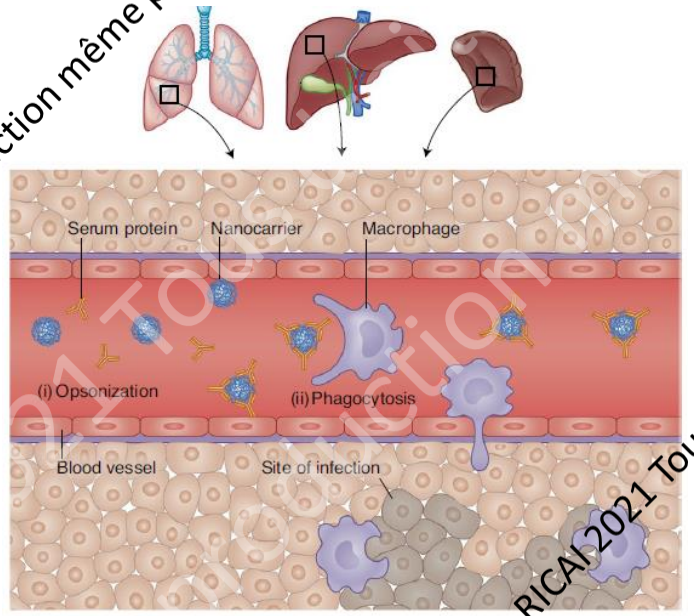
Nanomaterials to improve drug biodisponiblity

➡ To target the site of infection

Vascular permeability



Nanocarriers opsonization



Serum proteins adsorption → Phagocytosis → Tissue invasion

Kirtane, Nat Nanotechnol. 2021

Nanomaterials to improve drug biodisponiblity

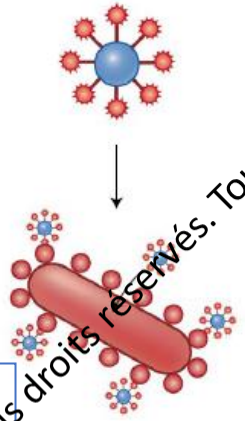
➡ To target the infectious agent

On microbial surface

Inside host cell

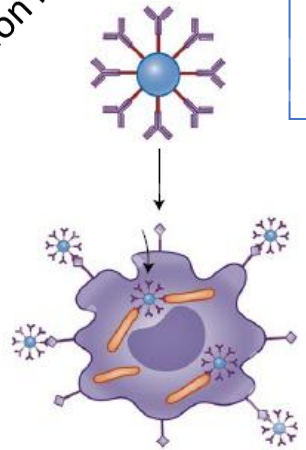
Trypanosoma brucei:
Pentamidine in PLGA functionalized with nanobodies

Arias, J Control Release, 2015.



Staphylococcus aureus:
Vancomycin-loaded nanoparticles functionalised with cyclic peptides

Hussain, Nat Biomed, 2018.



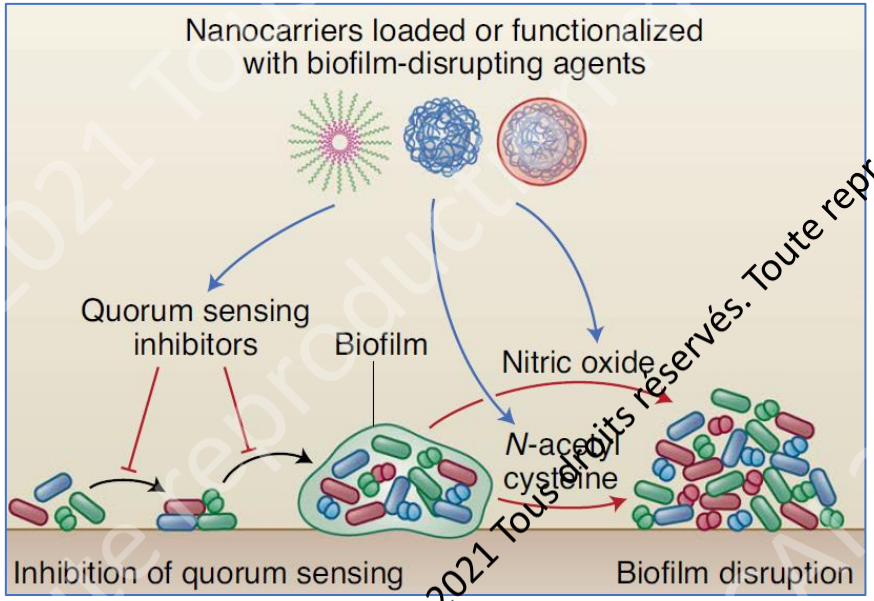
Macrophages:
Ciprofloxacin loaded mannose-functionalized liposomes

Chono, J Control Release, 2008.

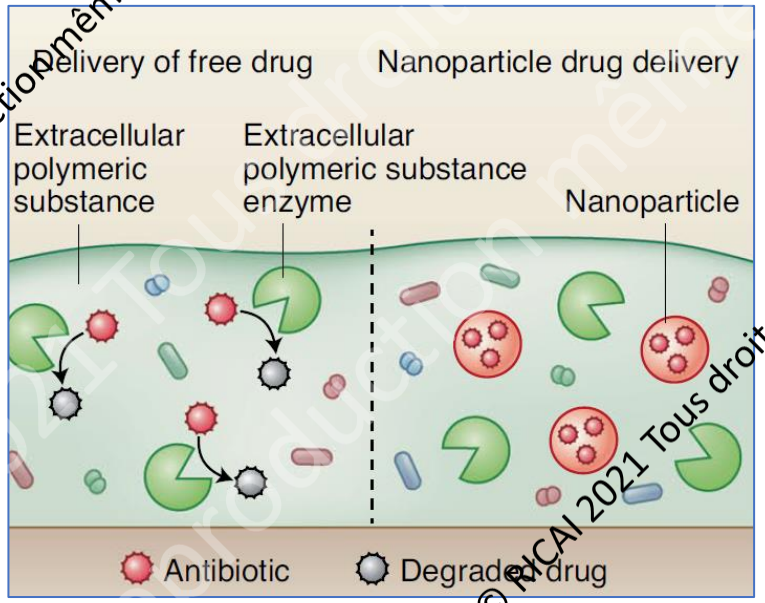
PLGA: Poly lactic-co-glycolic acid

Nanomaterials to overcome resistance mechanisms

➡ Disrupt biofilm infections



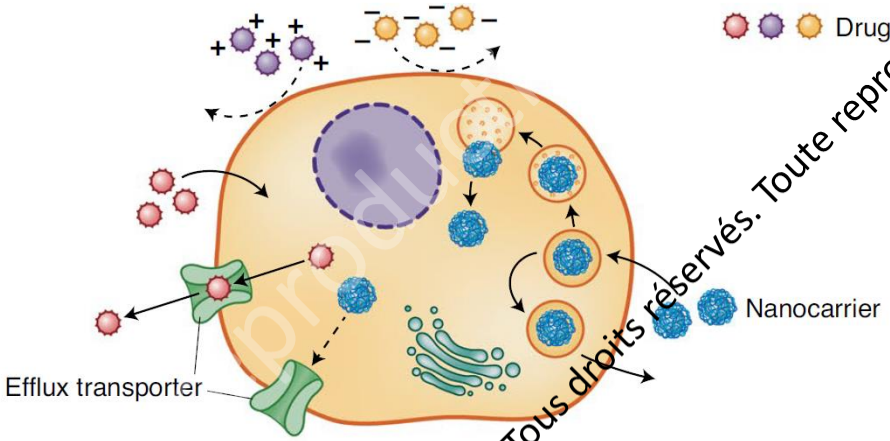
➡ Protect from drug-degrading enzymes



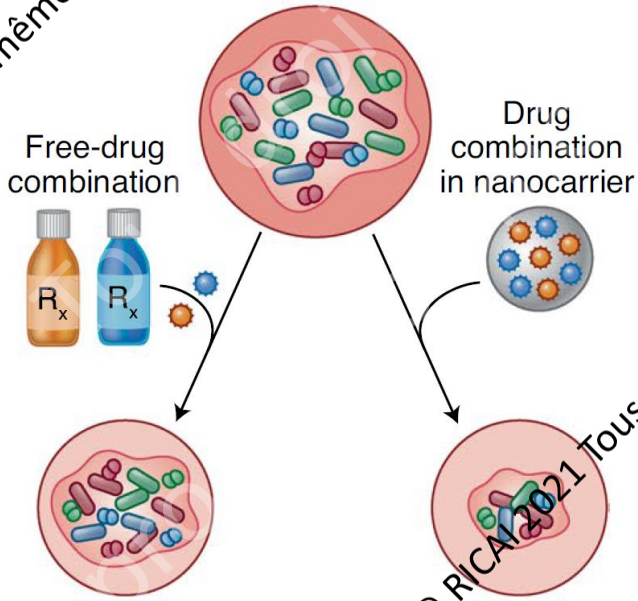
Kirtane, Nat Nanotechnol. 2021

Nanomaterials to overcome antibiotic resistance

➡ Accumulation into the host cell



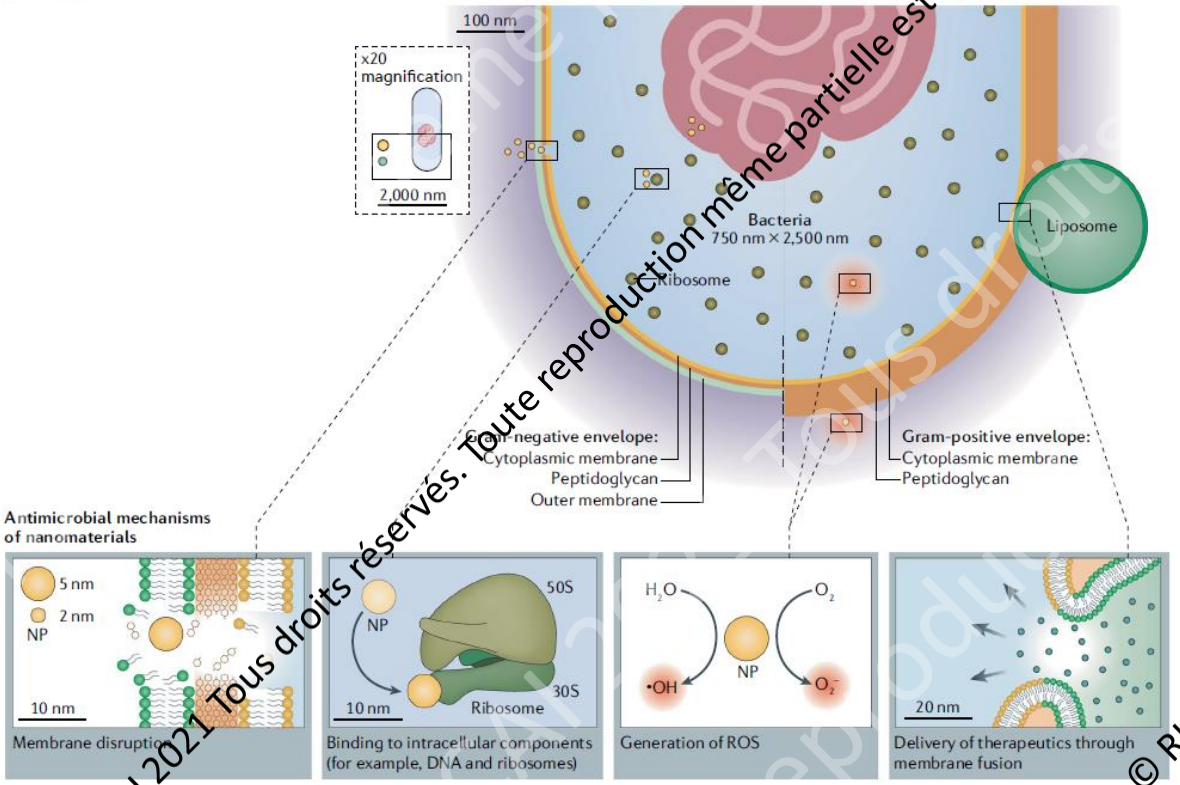
➡ Multiple drugs packaging



Kirtane, Nat Nanotechnol. 2021

Nanomaterials as therapeutic agent

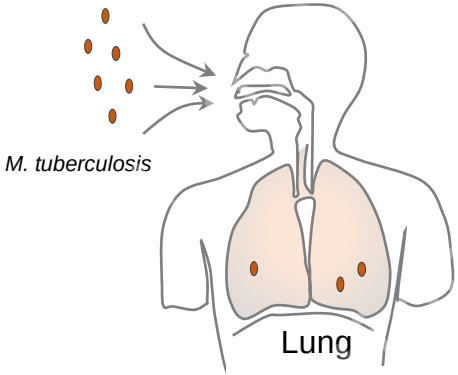
- Against the infectious agent

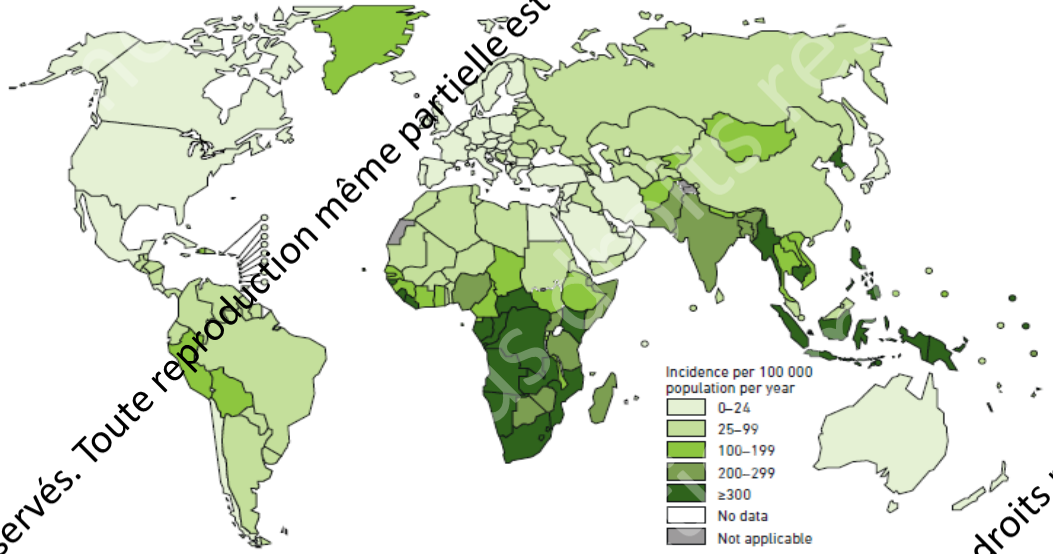


- As host-targeted therapy agent

Makabenta, Nat Rev Microbiol. 2021

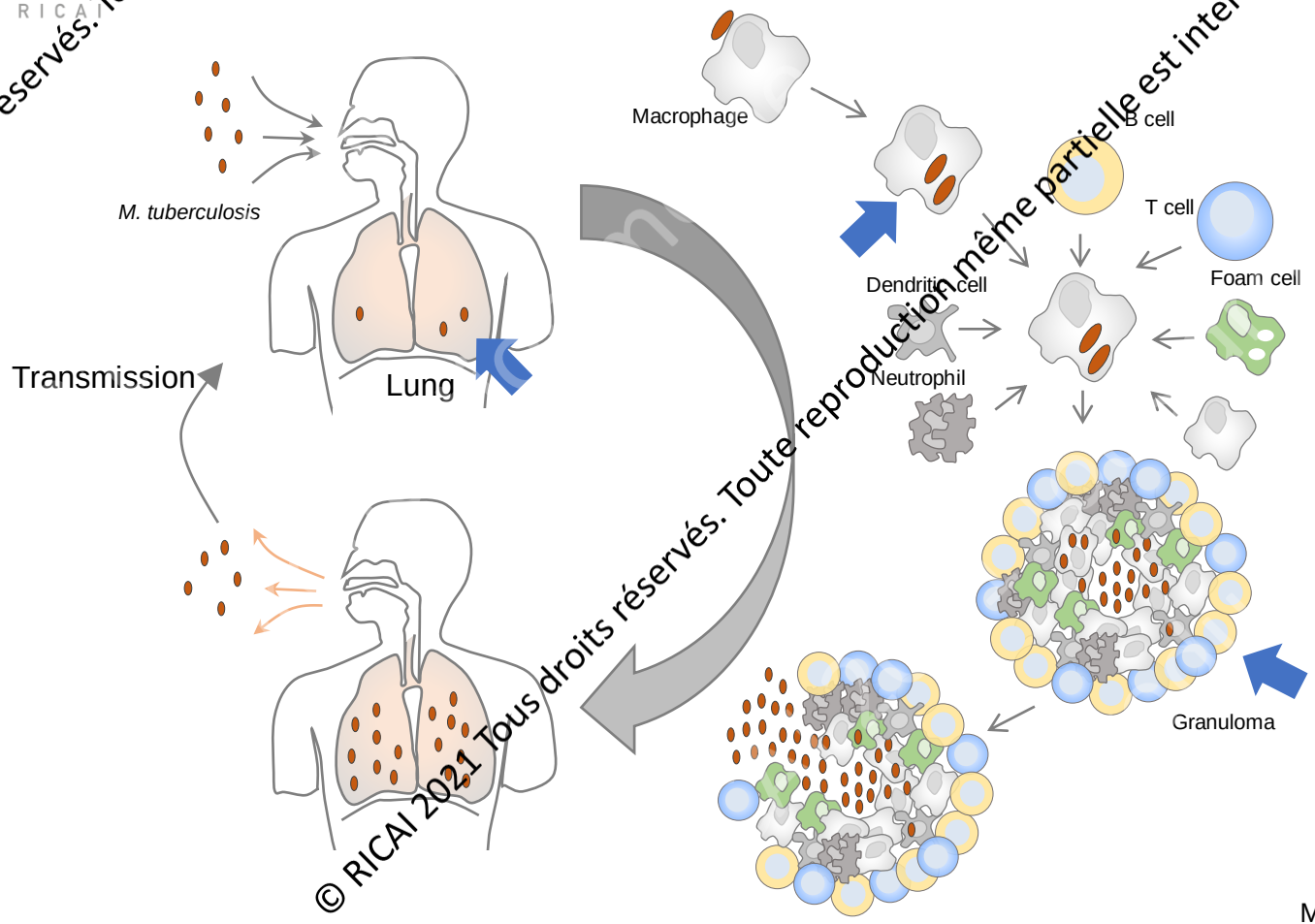
Tuberculosis : Infectious travel





- 10 million cases per year (1 – 2 million deaths)
- Lack of efficient vaccination
- Dramatic increase in drug resistant cases
- Fail of treatment (15,000 pills to treat MDR)

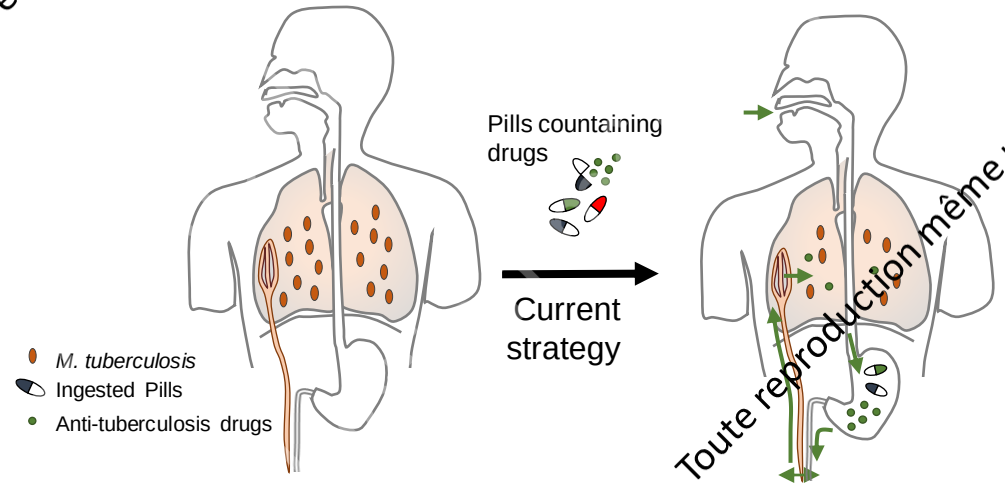
Tuberculosis : Infectious travel



Biodisponibility challenge:
- Infected organ
- Intracellular lifestyle
- Lesion penetration

Machelart, Drug Discov Today. 2017

Tuberculosis : Current treatment

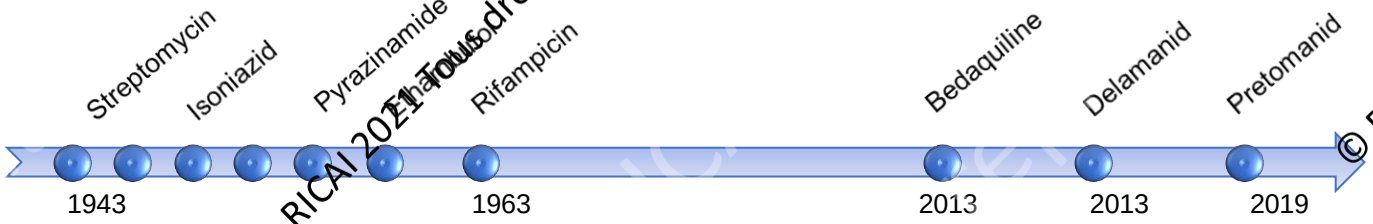


Standard treatment:
Daily 1st line drugs
6 months

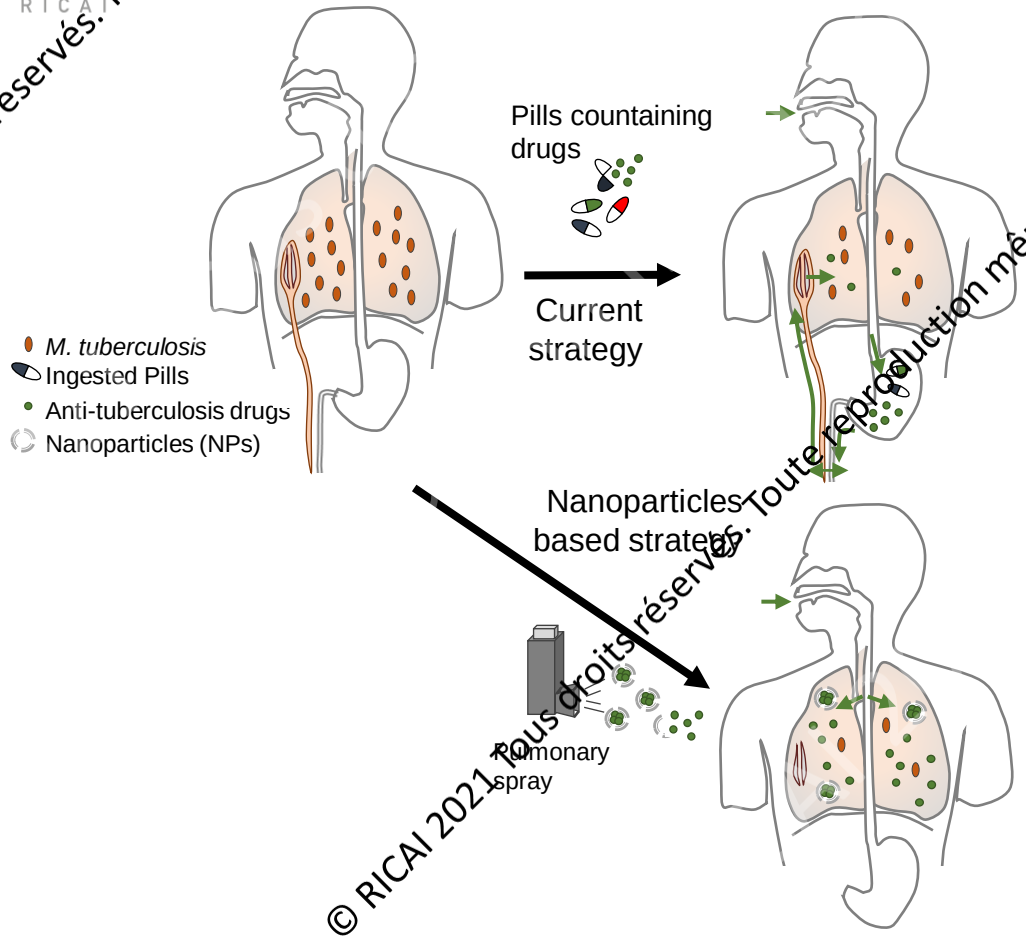
Isoniazid
Rifampicin
Pyrazinamide
Ethambutol

MDR-TB treatment:
Daily 2nd line drugs
2 years

Ethionamide
Fluoroquinolones
Aminoglycosides
Bedaquiline
Delamanid
Pretomanid

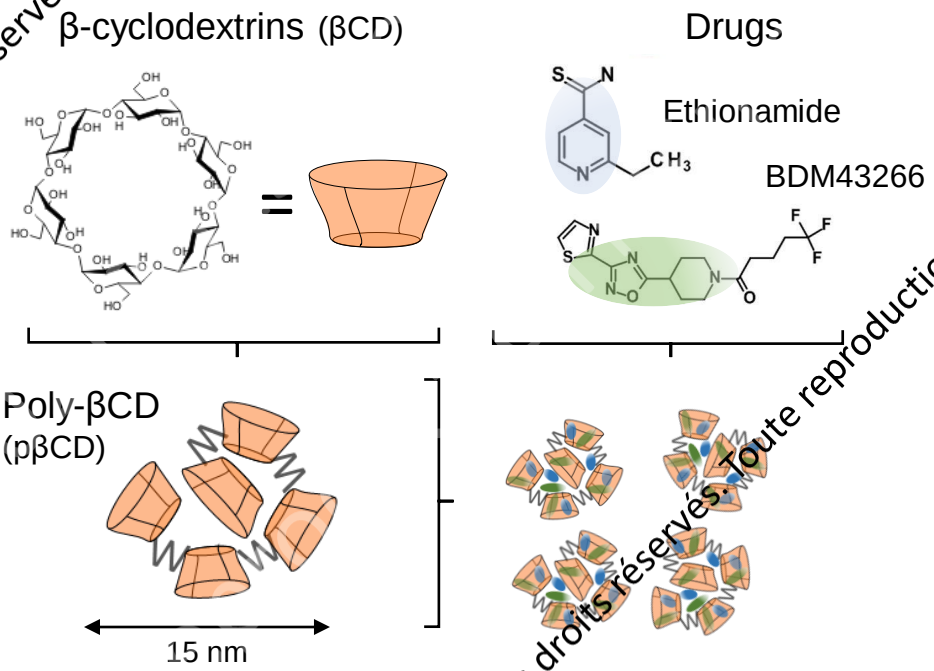


Nanomaterials to improve therapy



In the context of tuberculosis:
- Biodisponibility
- Treatment duration
- Antibiotic resistance
- Multi-therapy

Polymeric cyclodextrins

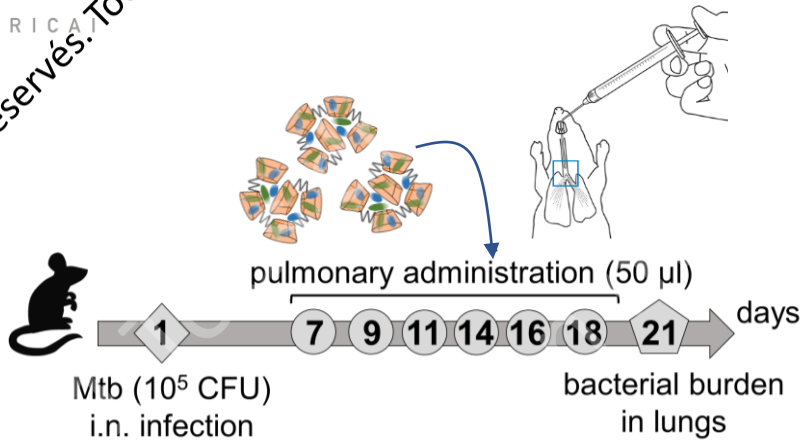


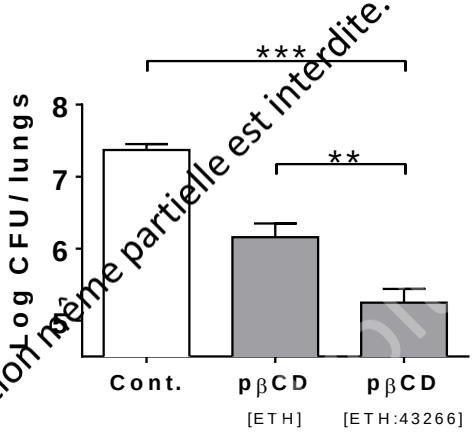
β-cyclodextrins (βCD):
- soluble
- low cost
- non soluble drugs incorporation
- non toxic
- widely used in industry (food, cosmetic)

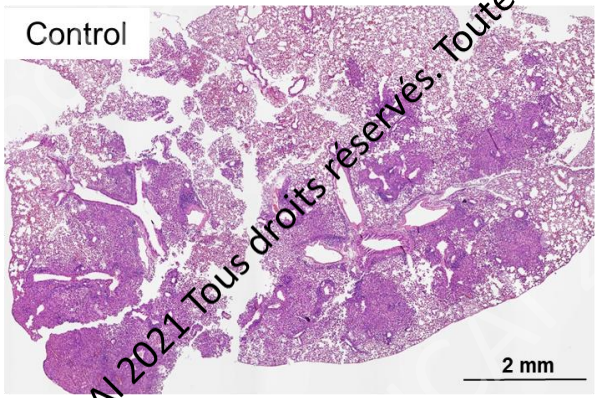
Poly-β-cyclodextrins (βCD):
- enhanced solubility
- Proper size for targeting macrophages
- allow nebulization
- non toxic (genotoxicity/*in vivo* assays)

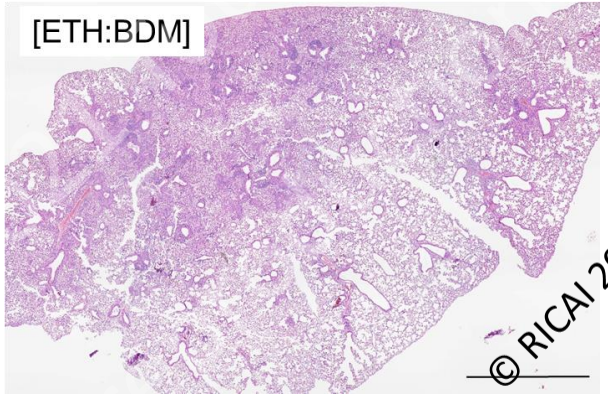
Non soluble drugs:
- Ethionamide (prodrug activated by EthA)
- BDM43266 (activator of EthA)

In vivo proof of concept





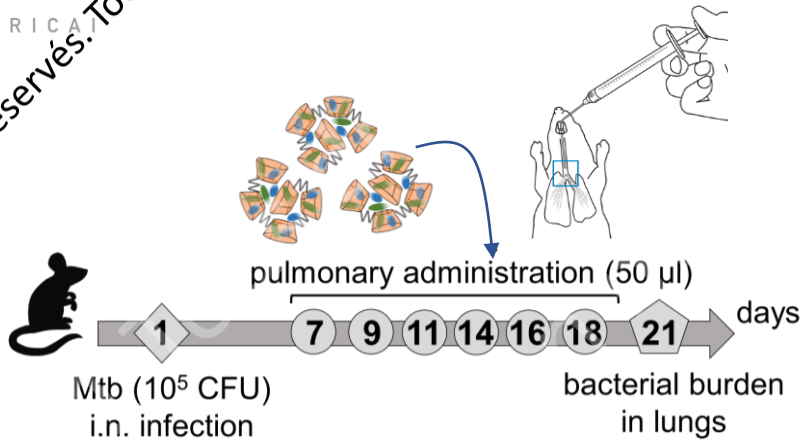


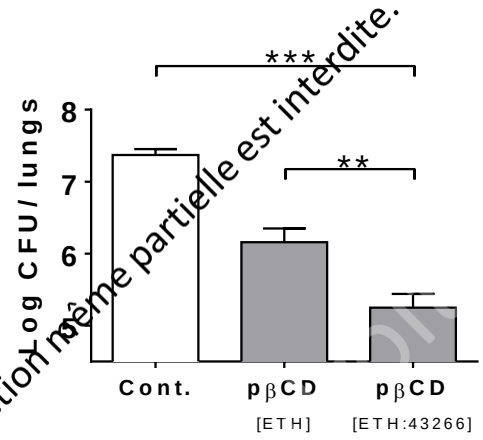


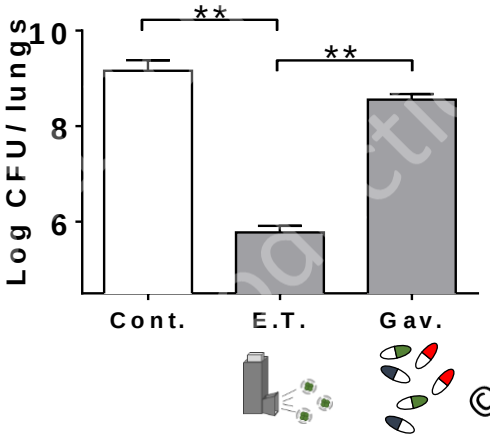
ETH : Ethionamide – 43266 : BDM

Costa-Gouveia, Scientific report. 2017
Villemagne, ACS Infect Dis. 2020

In vivo proof of concept





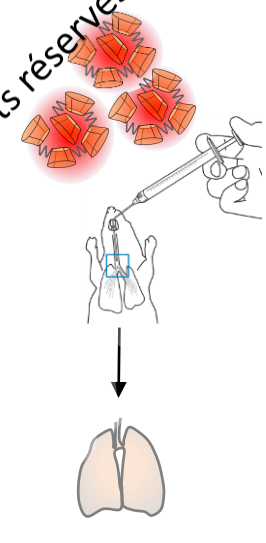


- Nanoparticles allow pulmonary administration

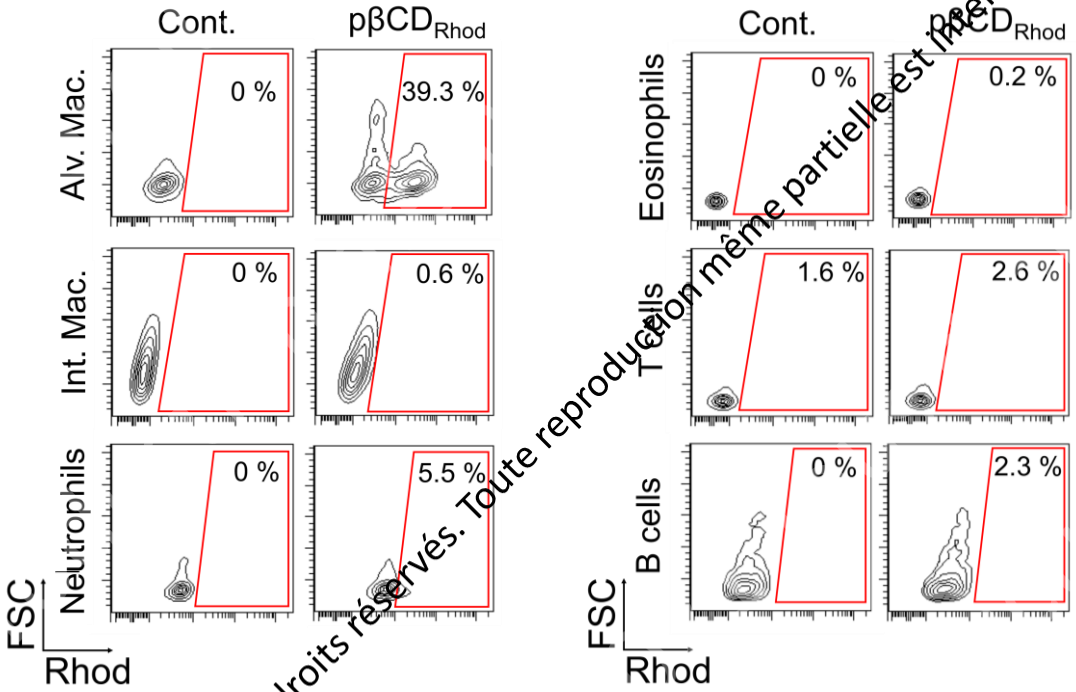
ETH : Ethionamide – 43266 : BDM - E.T.: endotracheal – Gav.: oral route

Costa-Gouveia, Scientific report. 2017
Villemagne, ACS Infect Dis. 2020

In vivo biodisponibility



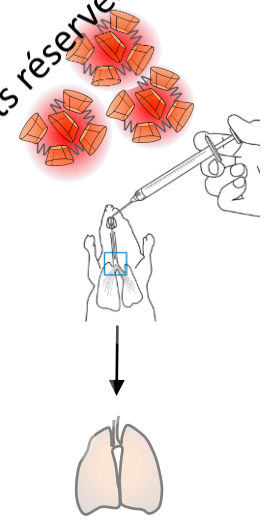
Flow cytometry



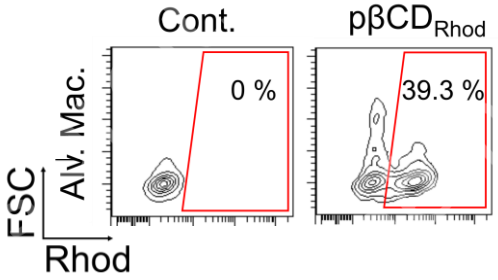
➡ Nanoparticles are engulfed by alveolar macrophages

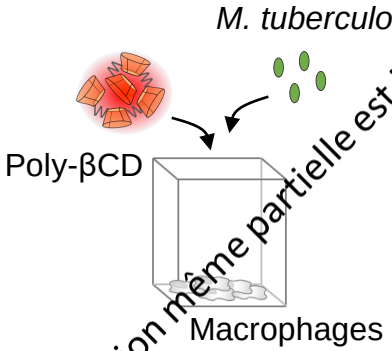
Machelart, ACS Nano. 2019

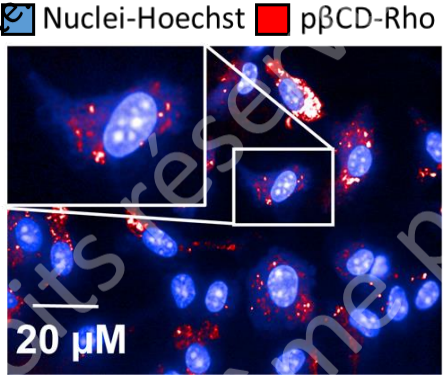
In vivo biodisponibility



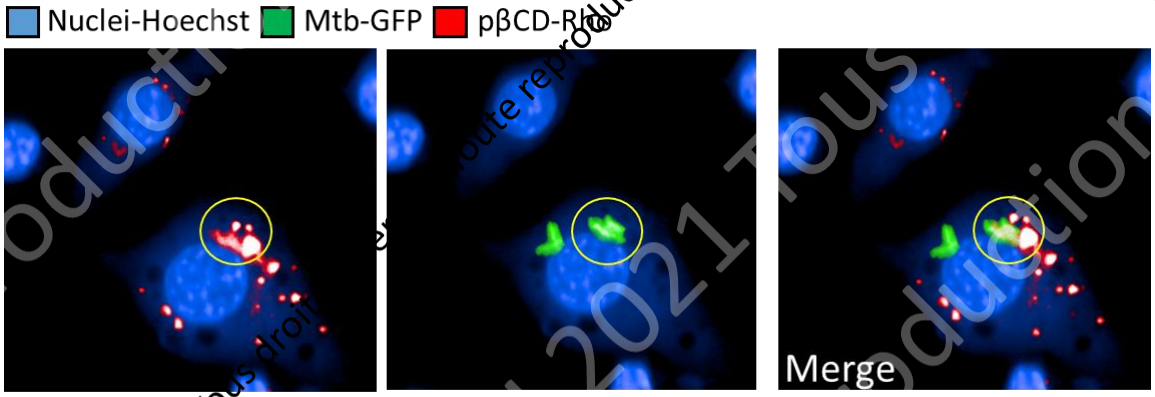
Flow cytometry







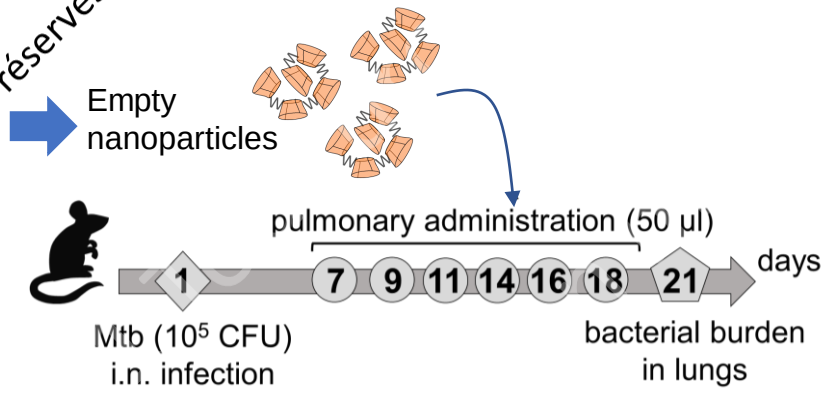
BMDMs (24 h, 2 mg/mL)

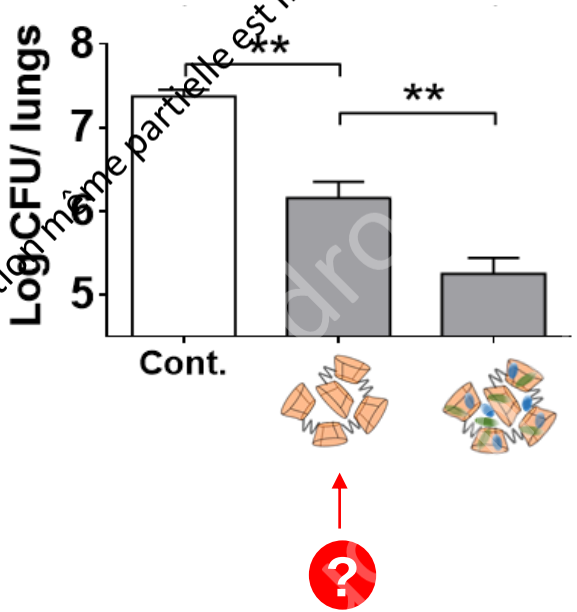


- Nanoparticles are engulfed by alveolar macrophages
- Nanoparticles colocalize with *M. tuberculosis*

Machelart, ACS Nano. 2019

In vivo proof of concept



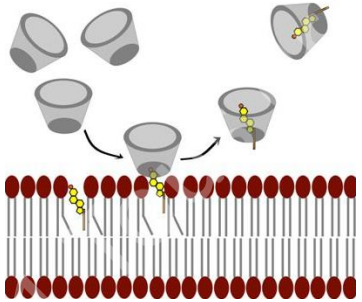


- Nanoparticles allow pulmonary administration
- Intrinsic antimycobacterial activity

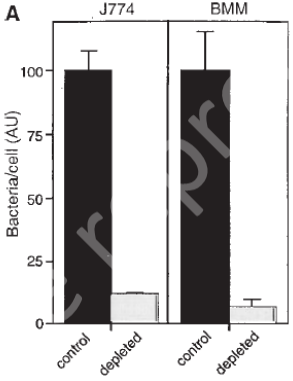
Machelart, ACS Nano. 2019

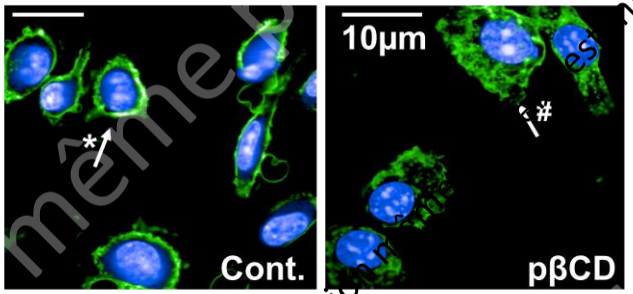
Nanoparticles impair bacterial uptake

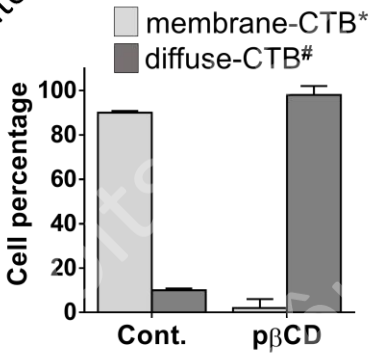
cyclodextrins deplete cholesterol

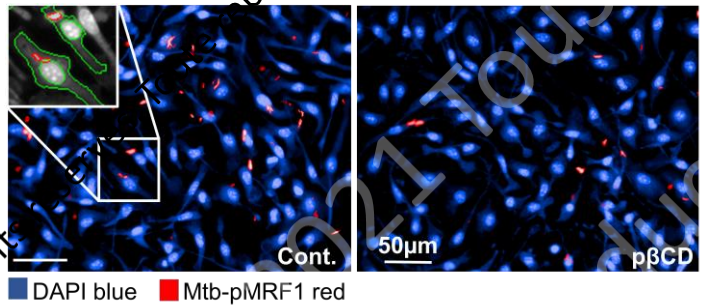


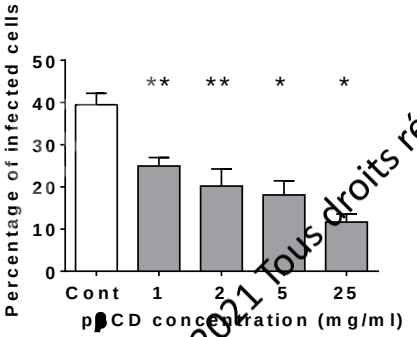
Mycobacteria use cholesterol to invade cell









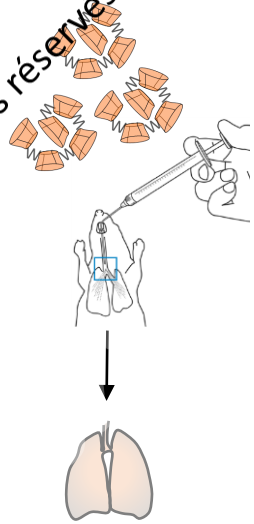


Christoforides, J Organic Chem 2018.

Gatfield, Science 2000.

Machelart, ACS Nano. 2019

Nanoparticles induce alveolar macrophages apoptosis



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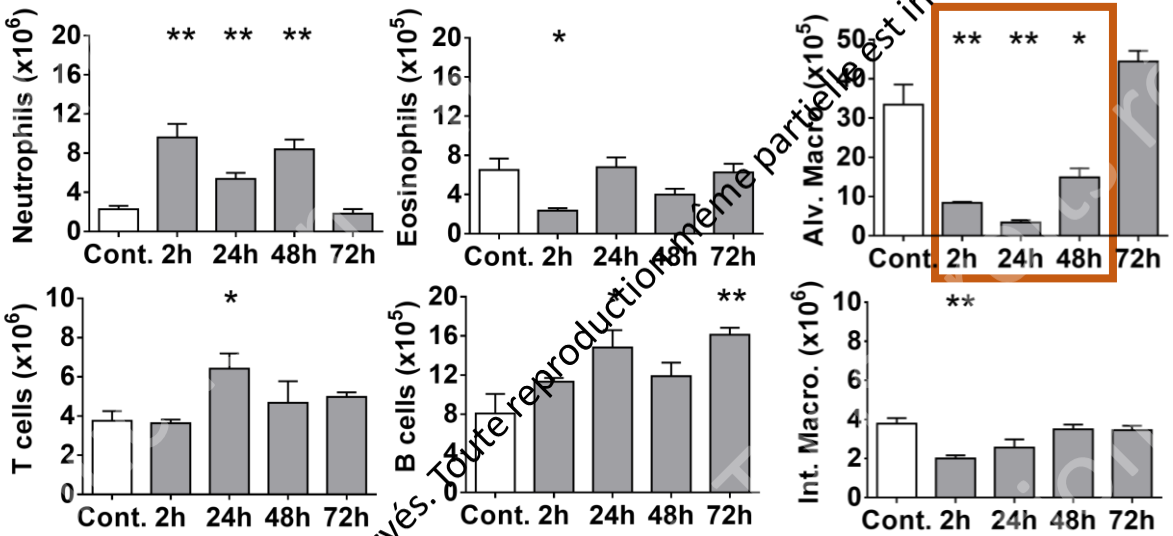

Machelart, ACS Nano. 2019

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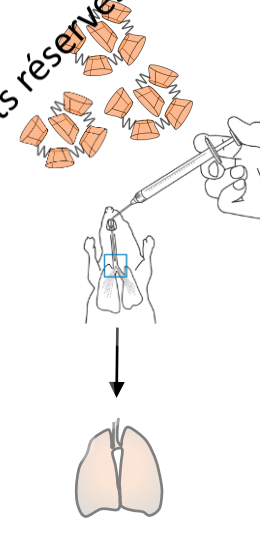
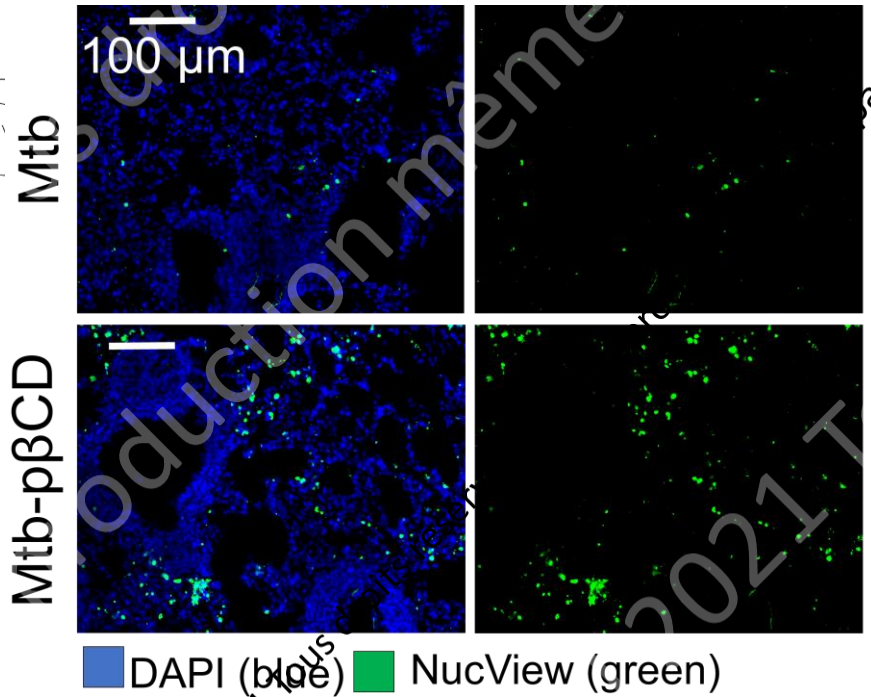
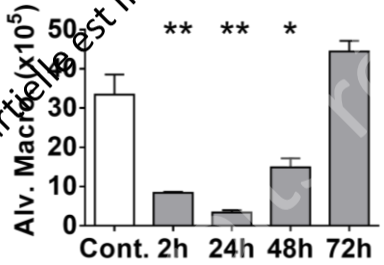
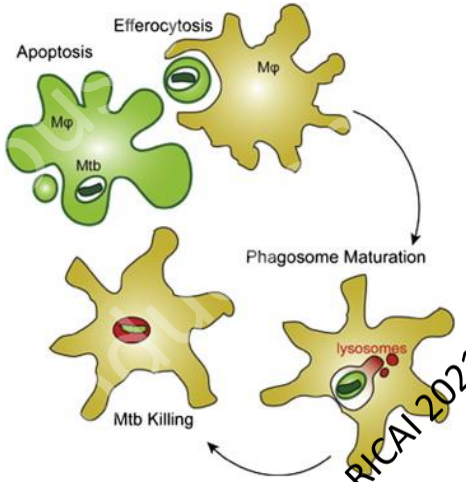


Flow cytometry





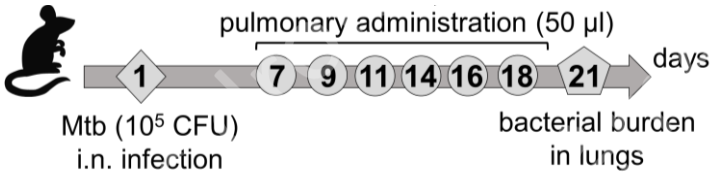


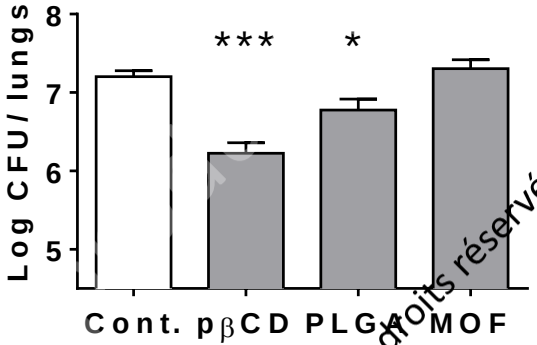
➡ Macrophages apoptosis could lead to efferocytosis

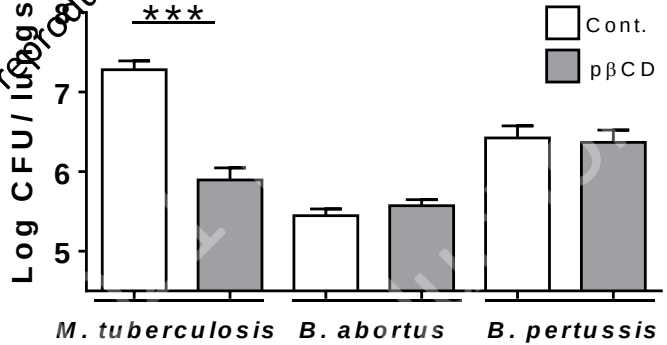
Martin, Cell Host & Microbe 2012.

Machelart, ACS Nano. 2019

Specific intrinsic activity against tuberculosis





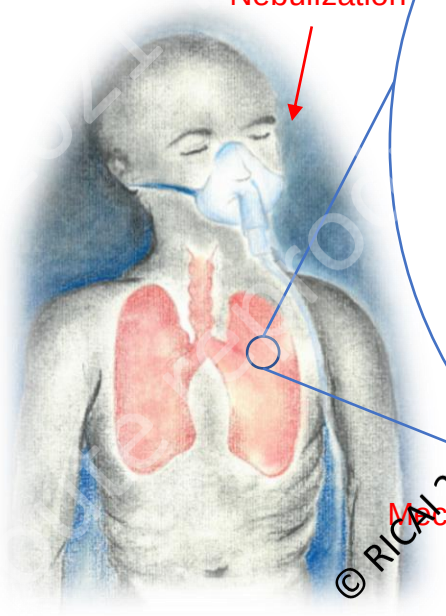


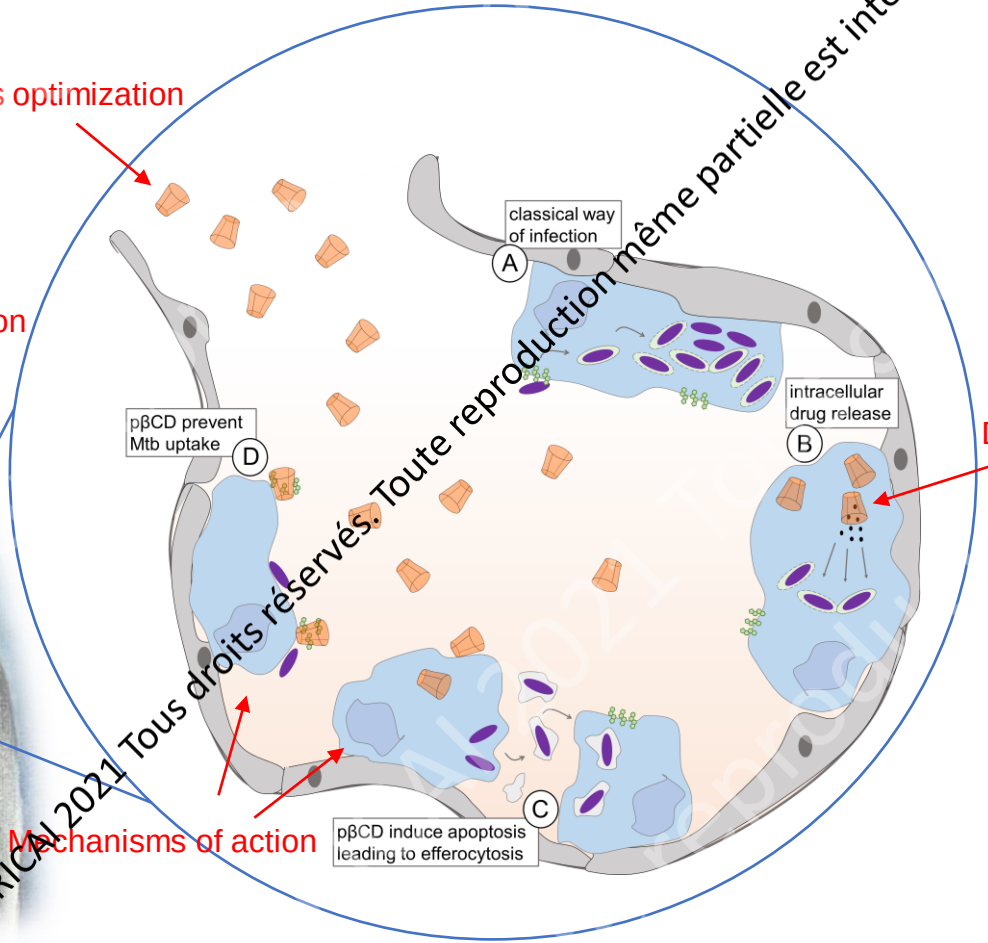
Machelart, ACS Nano. 2019

Summary

Nanopaticles optimization

Nebulization

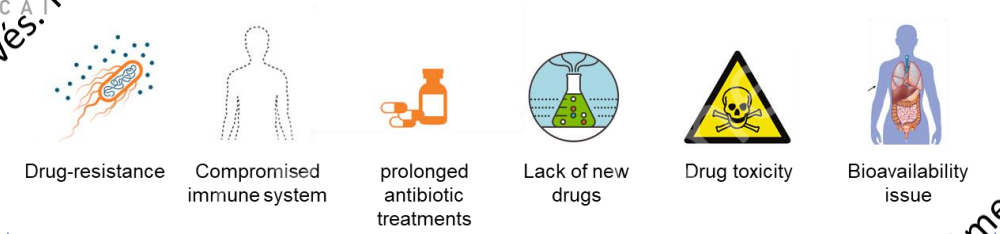


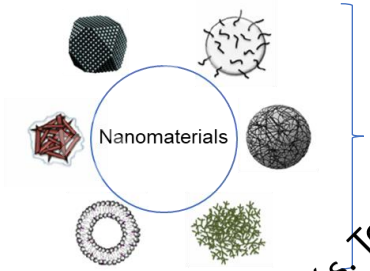


Drug combinaison

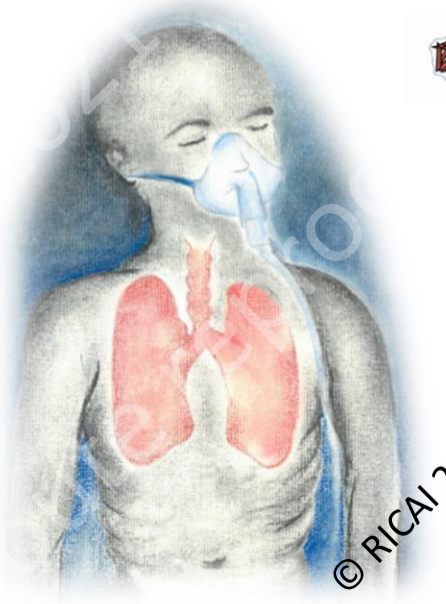
Mechanisms of action

Conclusion





- Improve drug biodisponiblity
- Overcome resistance mechanisms
- Allow multiple drugs encapsulation
- Antibacterial activity



Several challenges:
- Financial (product cost, development)
- Manufacturing (production, storage)
- Regulatory authorities
- *In vivo* models

Acknowledgment

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