Nanoparticles and rod-like particles for inhalation drug delivery

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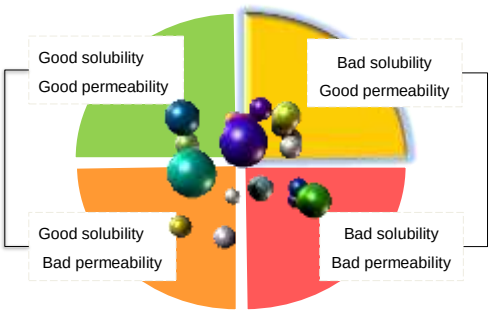
November 7th 2019

Gelatine, Dextrane
Alginate



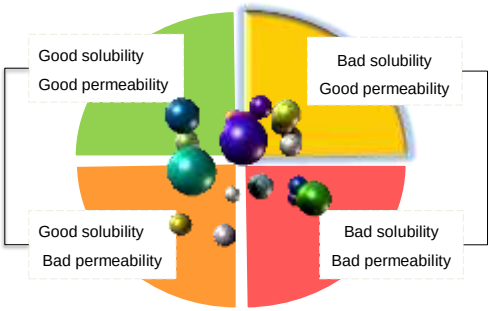
e.g. PLGA NP

Particulate carrier systems

Nano (nm)
Micro (µm)

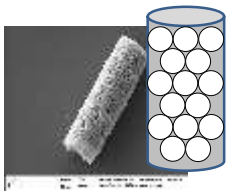
Chair of Biopharmaceutics and Pharm. Technology

Gelatine, Dextrane
Alginate

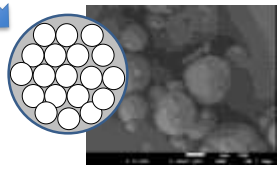


e.g. PLGA NP

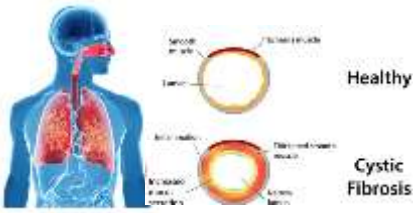
Particulate carrier systems



Biological
interaction



Cystic fibrosis

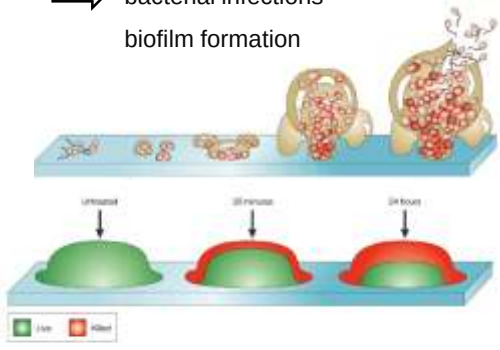


Current treatment drawbacks:

- Change of phenotype, alginate production, slow division
- Hindered therapy due to biofilm formation
- Antibiotic resistance
- No effective local therapy

- Autosomal recessive disorder
- Mutations in CFTR gene → defect chloride channel
- Abnormal thick mucus

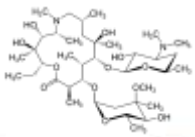
⇨ bacterial infections
biofilm formation

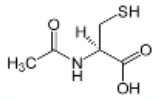


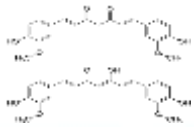
Cooper et, al., Nature. 2011, Davies. Nature Rev Drug Discov. 2003

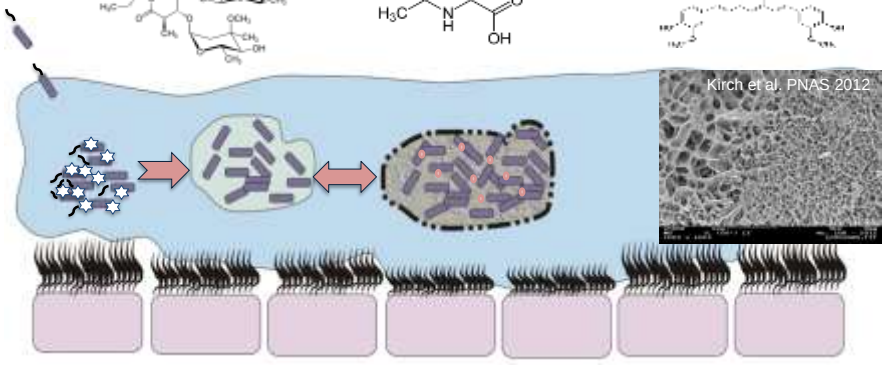
Treatment of CF

Drugs:	Antibiotics	Mucolytics	Antiphlogistics
	e.g Azithromycin	DNAse, N-Acetylcystein,…	Curcumin,…

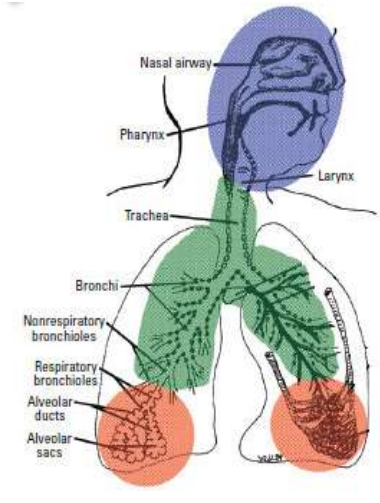


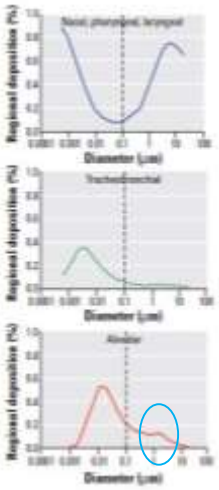






Deposition pattern of particles





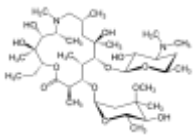
Nasal, pharyngeal, laryngeal Tracheobronchial Alveolar

Oberdörster, G, Oberdörster, E & Oberdörster, J (2005). Environmental health perspectives. 113. 823-39.

Treatment of CF with inhalable microparticles

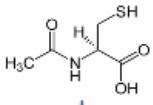
Drugs:

- Antibiotics
  e.g Azithromycin



Mucolytics

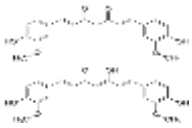
e.g. N-Acetylcystein,…



Spray drying

Antiphlogistics

Curcumin,…



2% Water

10 % EtOH

10 % MeOH

Not possible

10% Water

Matrix formation for spray drying

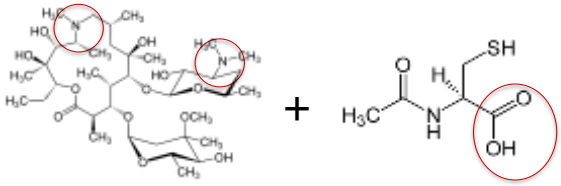
Drugs:	Antibiotics	Mucolytics	Antiphlogistics
	e.g Azithromycin	N-Acetylcystein,…	Curcumin,…
	hydrophobic	hydrophilic	hydrophobic

How to combine them ?

Matrix formation for spray drying

Drugs:

Antibiotics	Mucolytics	Antiphlogistics
e.g Azithromycin	N-Acetylcystein,…	Curcumin,…
hydrophobic	hydrophilic	hydrophobic

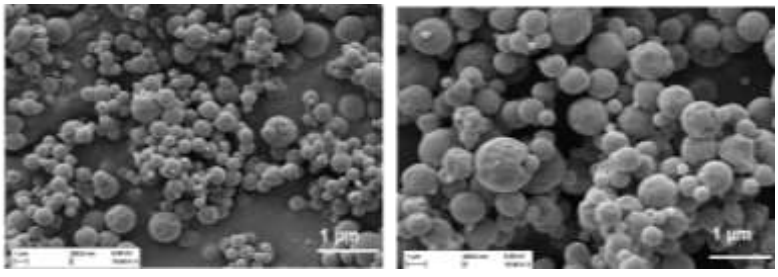


Complex formation by charges

Spray-drying of compounds

Drugs:

Antibiotics	Mucolytics	Antiphlogistics
e.g Azithromycin	N-Acetylcystein,…	Curcumin,…
hydrophobic	hydrophilic	hydrophobic

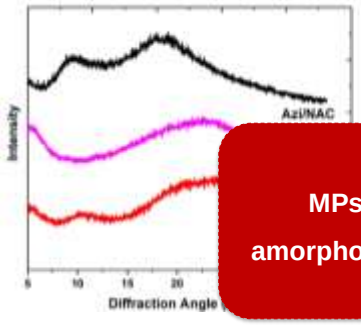


Particle characterization

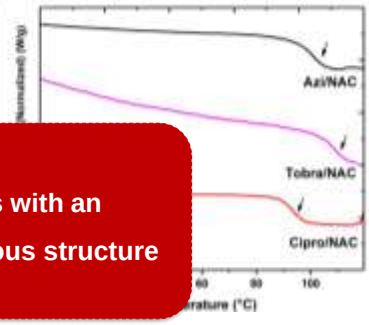
Glass transition temperature

Sample Name	Experimental T_g	Predicted T_g based
Azi/NAC	99.0 ± 0.9	66
Azithromycin	108.34 ± 0.5	-
N-acetyl-cysteine (NAC)	6.9 ± 1.9	

XRD



DSC

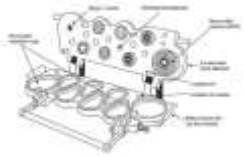


MPs with an amorphous structure

Lababidi et al, (2019) JCR

Characterization of SD Microparticles

Aerodynamic properties

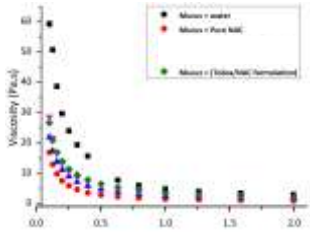


Formulation	AziNAC
MMAD [µm]	2.51 (± 0.06)
GSD	1.58 (± 0.04)
FPF [%]	68.83 (± 6.11)

High fine particle fraction

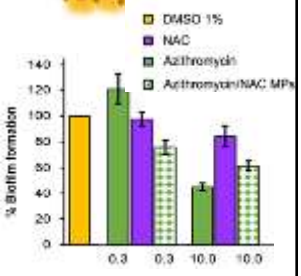
Viscosity

Plate – cone geometry



reduced mucus viscosity

Biological activity



reduced biofilm formation

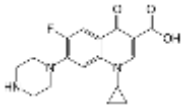
Lababidi et al, (2019) JCR

Treatment of CF

Drugs:

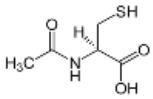
- Antibiotics

e.g Ciprofloxacin



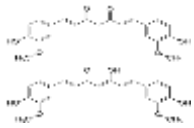
Mucolytics

DNAse, N-Acetylcystein,…



Antiphlogistics

Curcumin,…



hydrophobic

Embed in

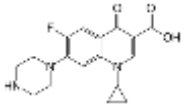
PLGA nanoparticles

Treatment of CF

Drugs:

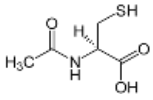
- Antibiotics

e.g Ciprofloxacin



Mucolytics

DNAse, N-Acetylcystein,…



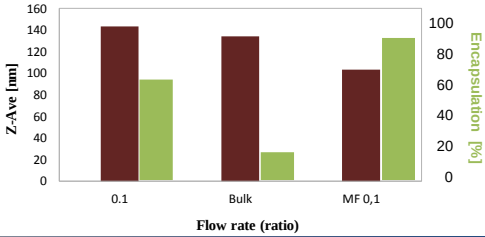
Antiphlogistics

Curcumin,…

Nanoparticle formation

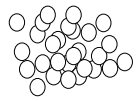
(µfluidics)

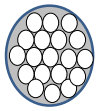
Production parameters to Size



Lababidi et al, Beilstein J Nanotech, accepted

Combining Nano and Micro



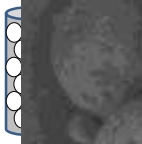


Spherical particles
(Spray drying)

20% NP fraction

Torge et al. Europ J Pharm Sci, 2017 104:171, Baghdan et al. Europ J Pharm Sci, 2019, 132:63

Spray-dried Particles

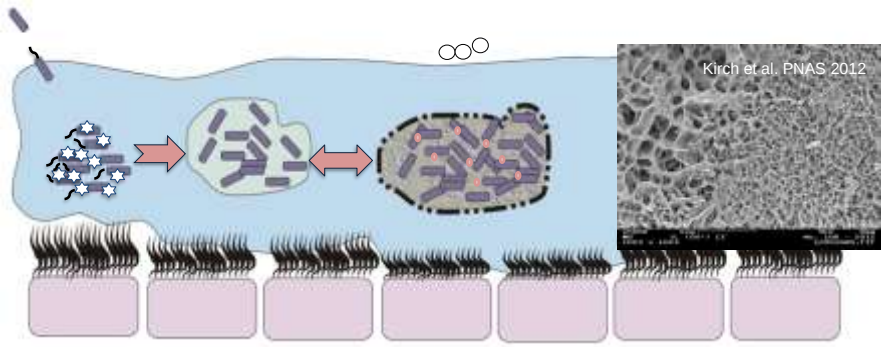


Cylin
(Tem

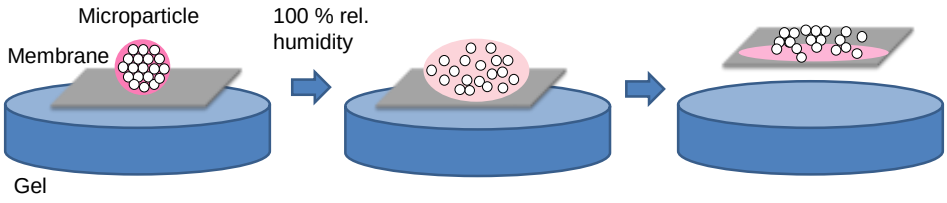
What do we need after inhalation?

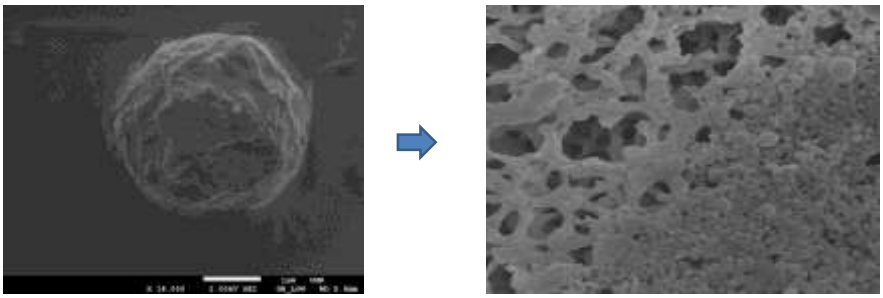
Deposition of the inhaled particle

What happens after landing?



Redispersibility in lung conditions





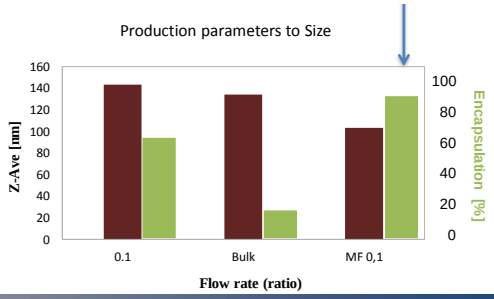
Treatment of CF

Drugs:

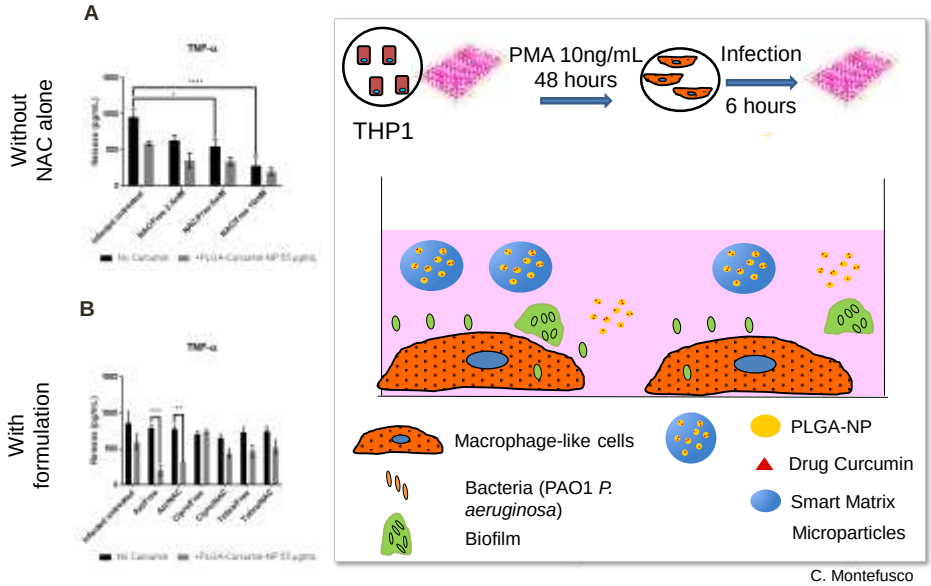
Antibiotics	Mucolytics	Antiphlogistics
e.g Azithromycin	N-Acetylcystein,…	Curcumin,…
hydrophobic	hydrophilic	hydrophobic

Nanoparticle formation (µfluidics)

Formulation	MMAD [µm]	GSD	FPF [%]
Azi/NAC	2.63 (±0.03)	1.53 (±0.06)	67.40 (±9.41)
Azi/NAC/NP	2.51 (± 0.06)	1.58 (±0.04)	68.83 (± 6.11)

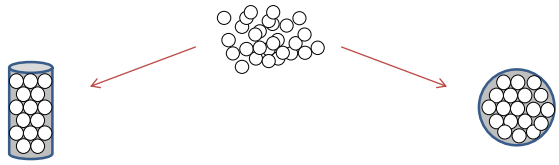


Functionality of drug-loaded nanoparticles



C. Montefusco

Microparticles for inhalation



Cylindrical particles
(Template technique)

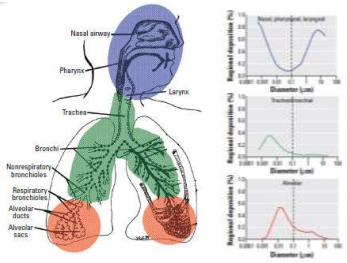
Spherical particles
(Spray drying)

Size influences deposition of drug carrier

Density

Shape

$$r_{ae} = r_g \sqrt{\frac{\rho}{\chi}}$$



- Nasal, pharyngeal, laryngeal
- Tracheobronchial
- Alveolar

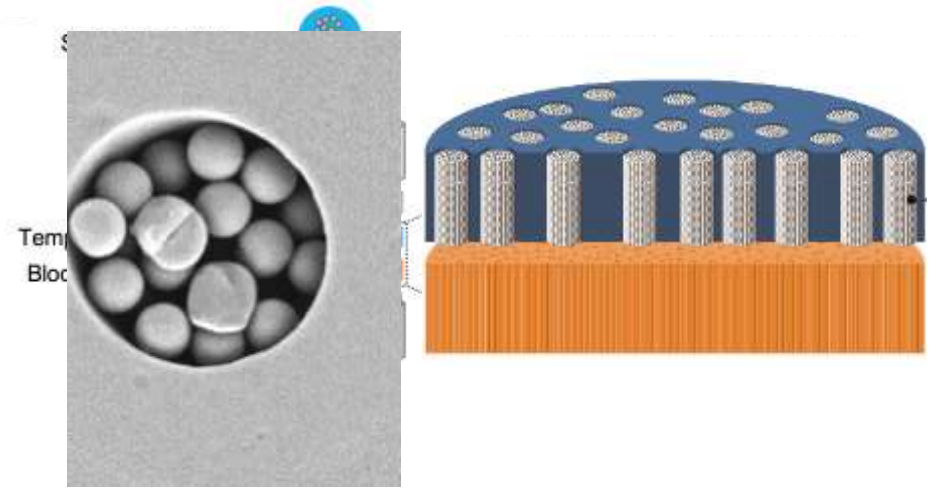
Shape & size influence biodistribution/ uptake

How to prepare?

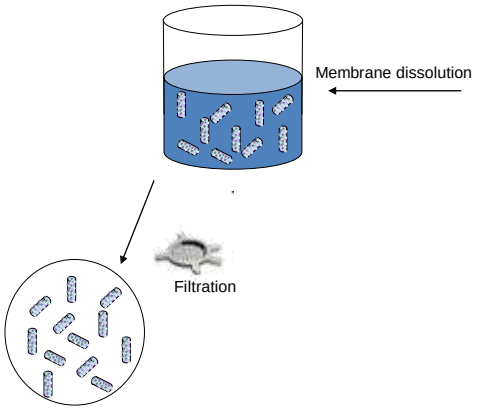
Why to prepare particles?

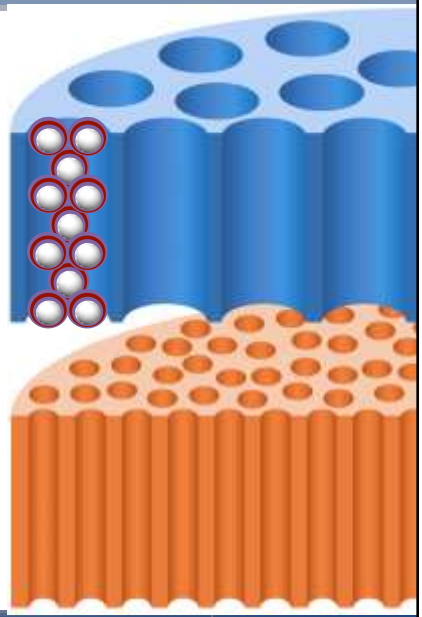
- Can be inhaled (powder inhalator)
- MΦ clearance can be modified (aspect ratio)
- For same diameter higher volume to be loaded

Production Method

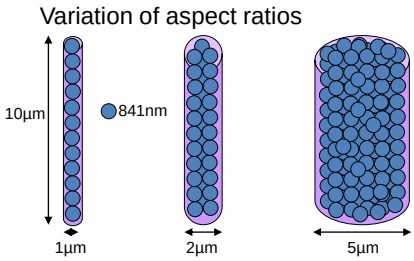


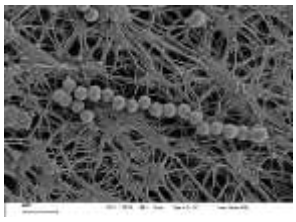
Stabilization by LbL technique and harvest



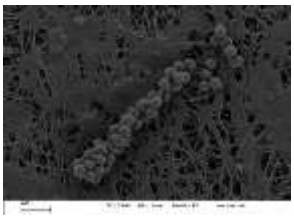


Size variations of cylinder particles





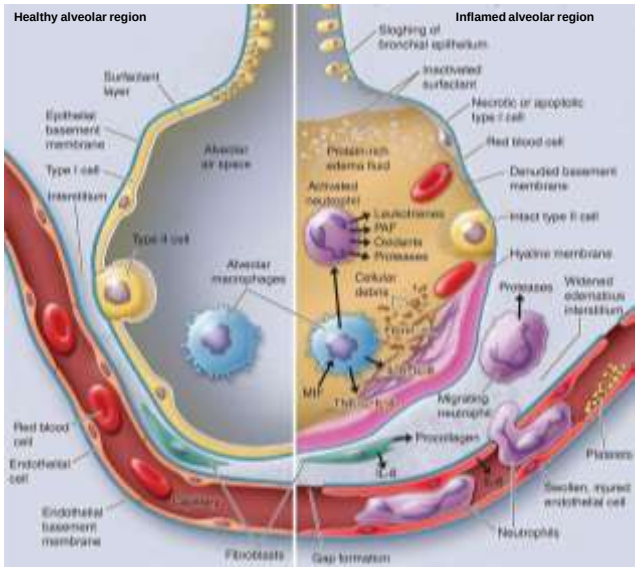
SiO_2 (841nm) +3bilayers PAH/PSS in 1µm PC-Membrane



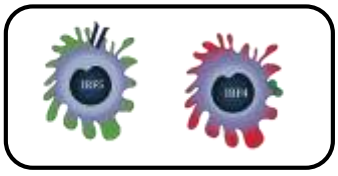
SiO_2 (841nm) + 5 and +3bilayers PAH/PSS in 2µm PC-Membrane

SiO_2 (841nm) +5 and +3bilayers PAH/PSS in 5µm PC-Membrane

Impact of Macrophages



Delivery System Requirements



Therapeutic Approach

Genetic Modulation of Macrophages

Delivery system – rods with

PE(+)

Polyethylenimine, Chitosan

DEAE-Dextran

PE(-)

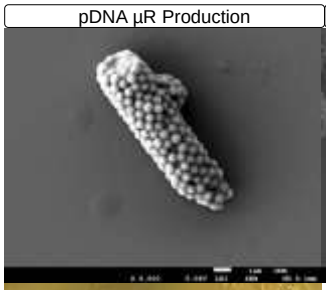
Dextran sulfate

pDNA

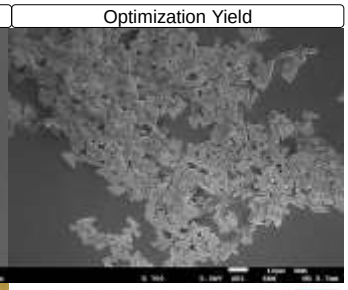
Boorsma et al. 2013

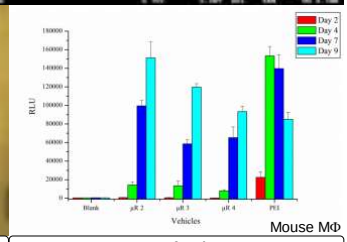
Microrods as Gene Delivery Plattform

pDNA µR Production



Optimization Yield





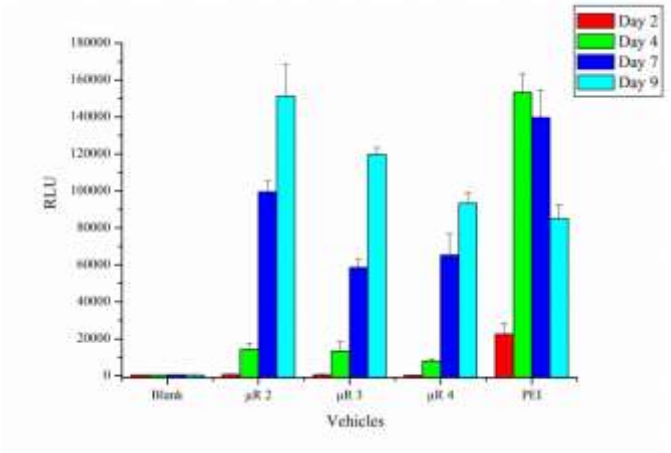
Mouse MΦ

Optimization *in vitro* Performance

Transfection

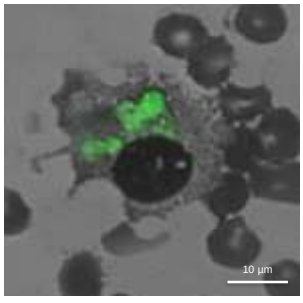
Microrods as Gene Delivery Plattform

pDNA µR Production | Optimization Yield

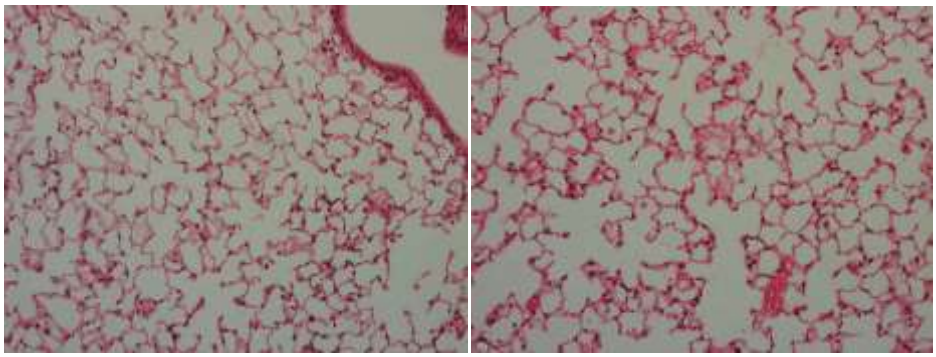


Optimization *in vitro* Performance | Transfection

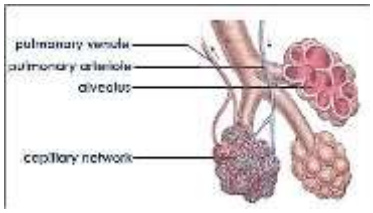
in vivo Studies



in vivo Studies – Histology



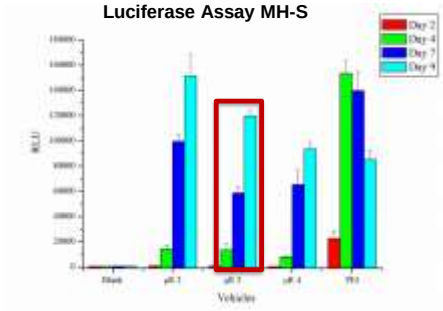
Day 1 Day 9

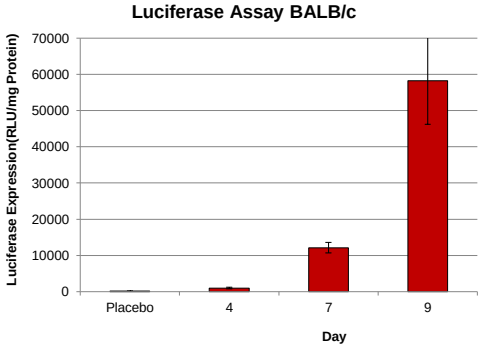


Park et al. 2012

Möhwald et al. (2017) Adv Healthcare Mater

in vivo Studies – Luciferase Assay

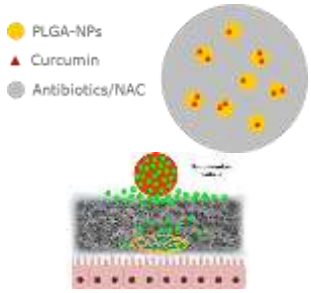




Möhwald et al. (2017) Adv Healthcare Mater

Summary

- Preparation of multifunctional particles
  - Inhalable particle
  - Fully active MP matrix
  - Incorporation of drug loaded nanoparticles



- Preparation of rod-like particles
- Loading with genetic material
- Transfection of macrophages *in vitro* & *in vivo*

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Thank you
for your attention