Lea Ann Dailey
Prof. of Pharmaceutical Technology and Biopharmacy
Phospholipid Research Center Seminar, 29 July 2026

Accommodation wanted!

Finding a good home for poorly soluble drugs to treat lung infections

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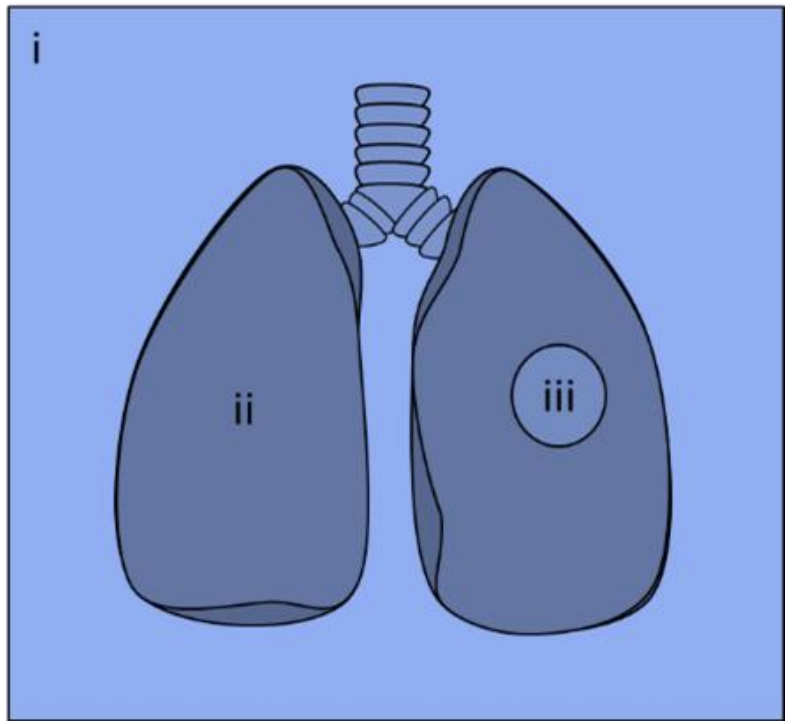
Promises of anti-infective delivery to the lung



Maximise drug exposure in the lung

⇩

Improved anti-infective efficacy

⇩

Fewer side effects

⇩

Reduced resistance

Challenges in anti-infective delivery to the lung

①	②	③	④
High dose lipophilic APIs	Lung retention	Limited formulation excipients	Dose requirements
⇩	⇩	⇩	⇩
Accumulation + non-specific inflammation	Fast clearance of lipophilic APIs	No tox data Dilution of drug	Unknown scaling factor

ANTI-TB

Antibiotic-loaded nanocarriers for therapeutic inhalation against tuberculosis

Bundesministerium für Bildung und Forschung

Forschungszentrum Borstel
Leibniz Lungenzentrum

Fraunhofer ITEM

KIT
Karlsruher Institut für Technologie

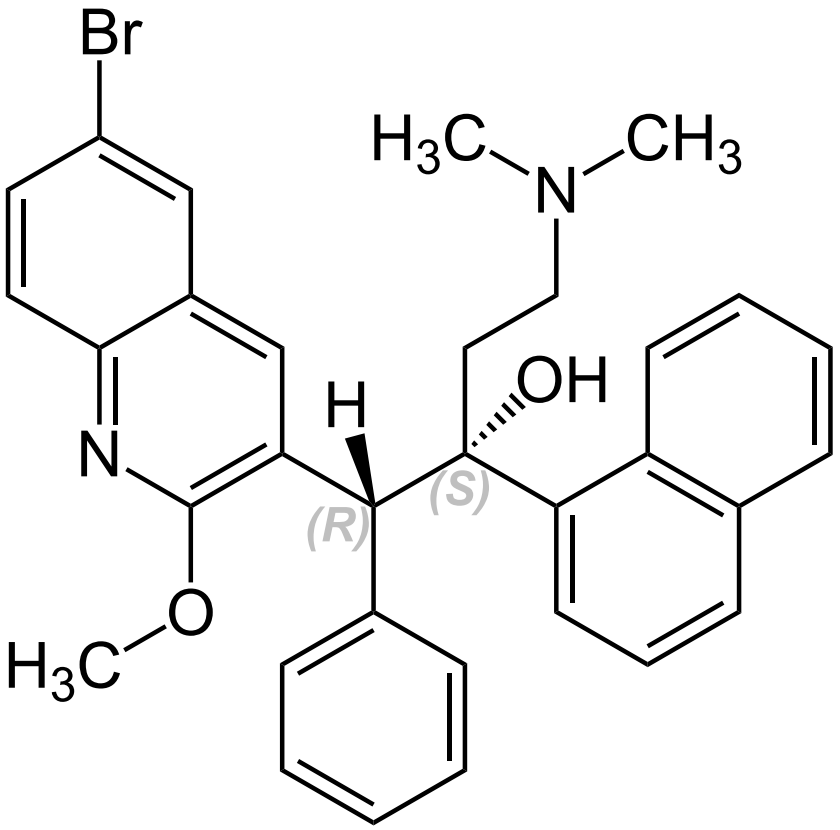
MARTIN-LUTHER-UNIVERSITÄT
HALLE-WITTENBERG

HIPS
HELMHOLTZ
Institut für Pharmazeutische Forschung Saarland

RODOS BIOTARGET

Lipophilic compounds chosen for study

Low solubility
0.002 µg/mL



BEDAQUILINE

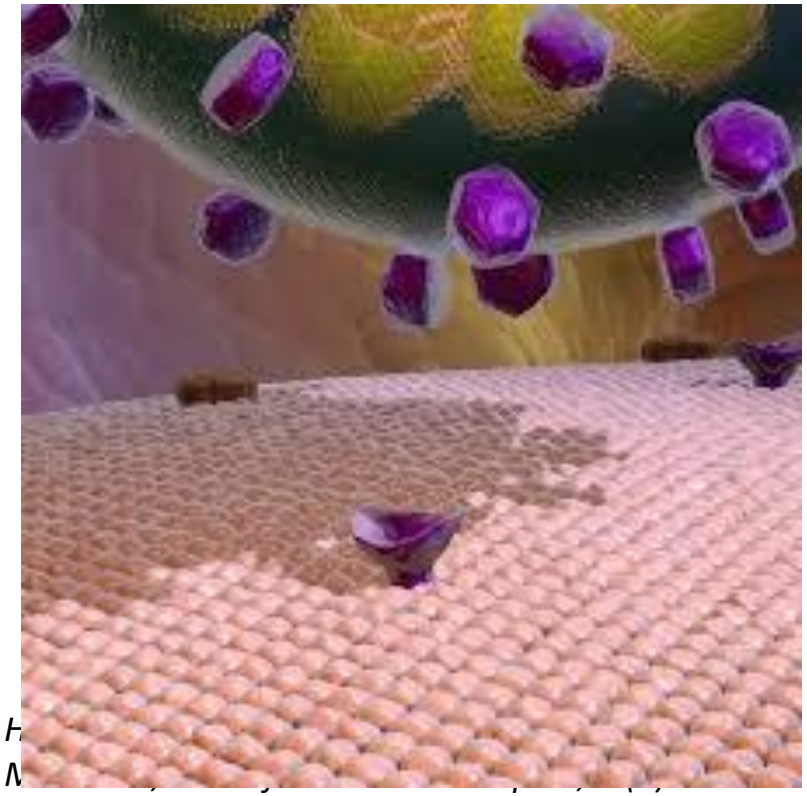
Log P
7.74

oral BA
~90%

CAD
QT
prolongation

Formulation development

RODOS BIOTARGET

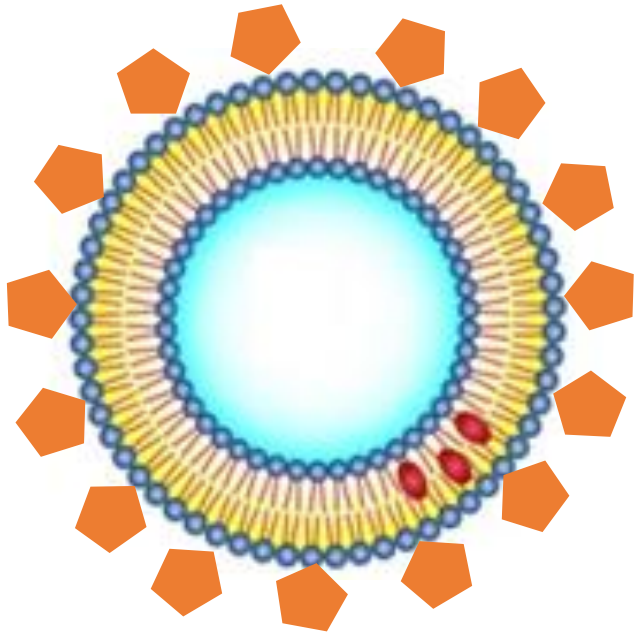


Fucosylated liposomes

- Target C-Lectin type receptors
- Human dendritic cells and monocytes
- DMPC:DMPG (2:1) liposomal composition
- 8 mol% cholesterol-fucose conjugate
- Lipid:BDQ mol ratio = ~15:1

Durán V, J Control Release. 2021 Jun 10;334:201-212. doi: 10.1016/j.jconrel.2021.04.012.

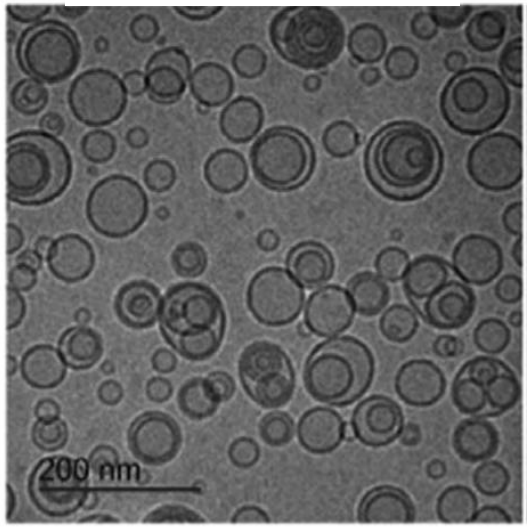
Liposomal bedaquiline for inhalation

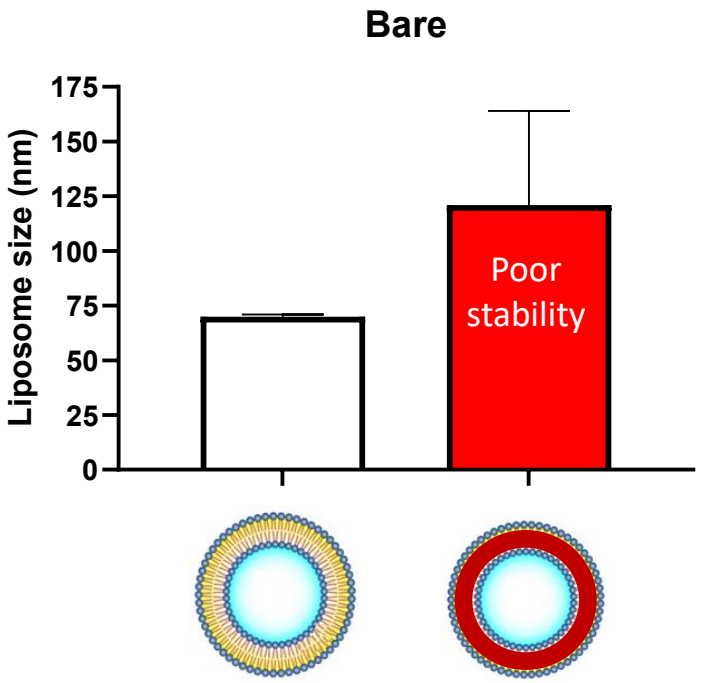


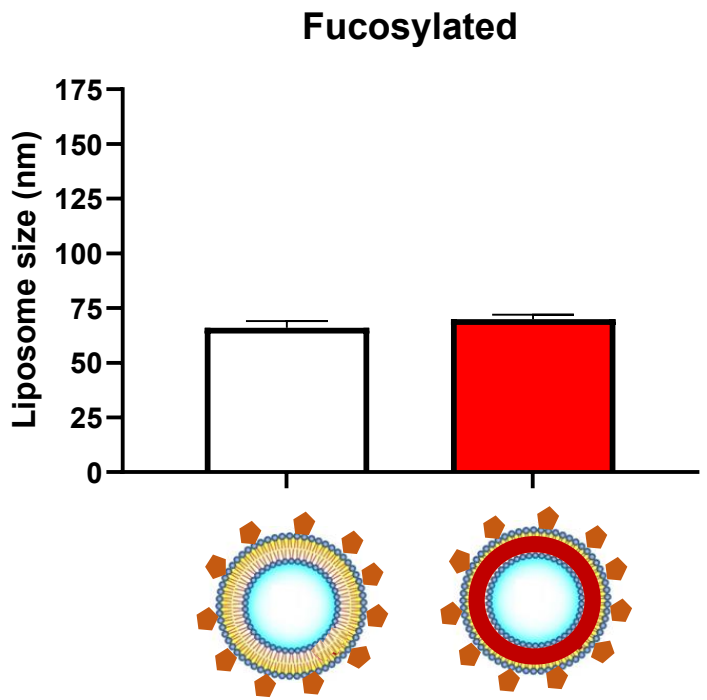
liposomes

- Drug solubilization: > 4 mg/mL
- Higher applicable doses with nebulization: 40 - 50 mg in one sitting
- No accumulation of undissolved drug in the lung
- Lung retention for improved efficacy
- Possibility for drug targeting?

An unexpected advantage of fucosylated liposomes



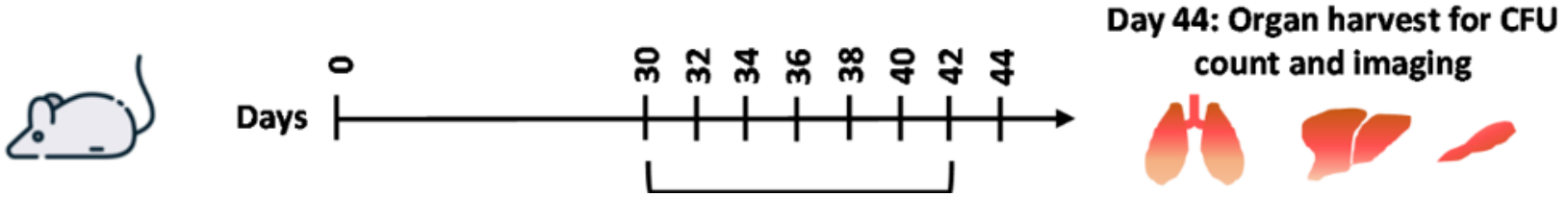




n=6

Huck et al (2021) https://doi.org/10.1002/adhm.202102117,
Marwitz F, ACS Infect Dis. 2024 Sep 13;10(9):3222-3232. doi: 10.1021/acsinfecdis.4c00192.

How active is liposomal BDQ against TB?



Infection model	Treatment groups (n=5)	Administration	Endpoints
Mtb H37Rv (100 CFU,aerosol) C3HeB/FeJ mice		intranasal two weeks every 2nd day 5 mg/kg	CFU in lung & spleen

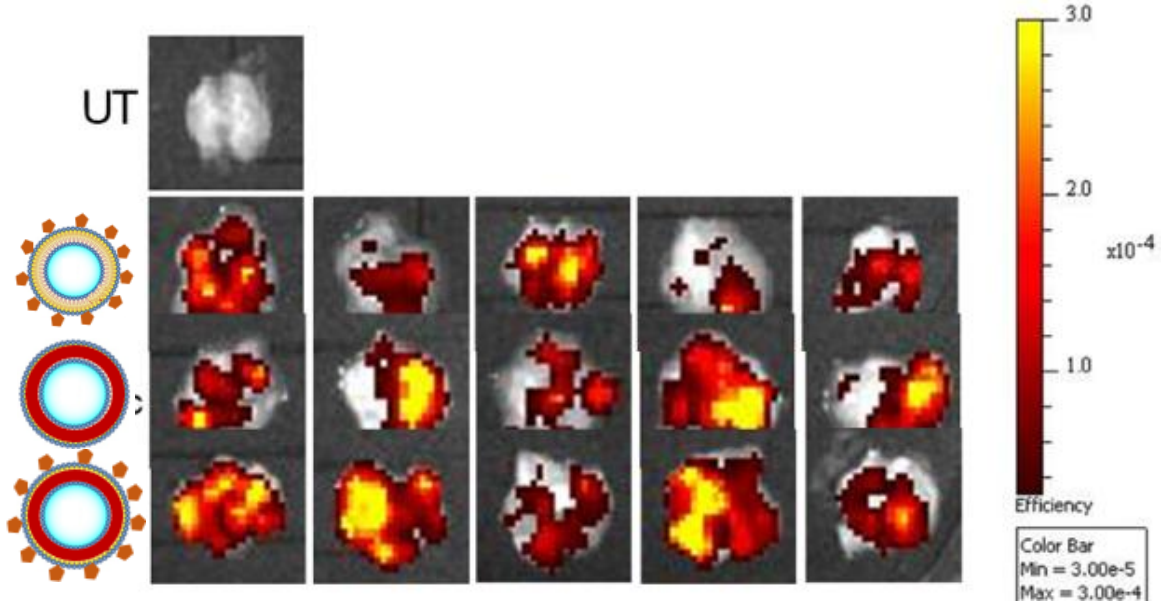
Why intranasal instillation?

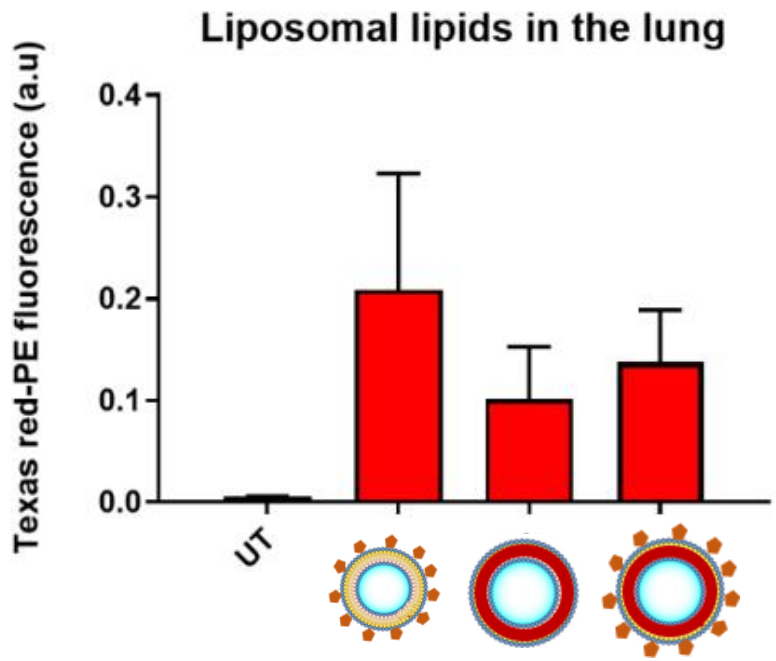
Less invasive for multiple daily dosing

(required by ethics committee)

Marwitz F, ACS Infect Dis. 2024 Sep 13;10(9):3222-3232. doi: 10.1021/acsinfecdis.4c00192.

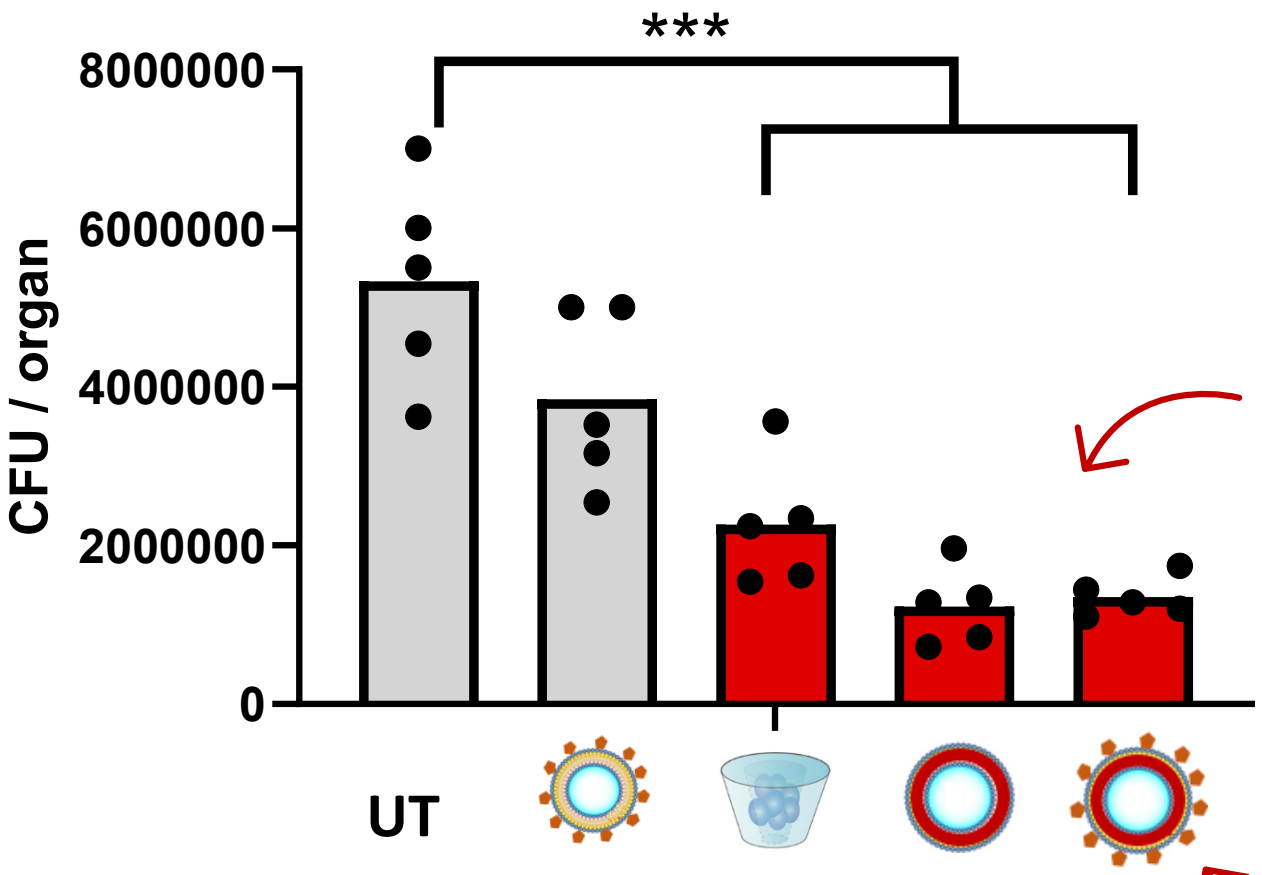
Does intranasal dosing reach the lung?





Marwitz F, ACS Infect Dis. 2024 Sep 13;10(9):3222-3232. doi: 10.1021/acsinfecdis.4c00192.

M. tuberculosis burden in the lung



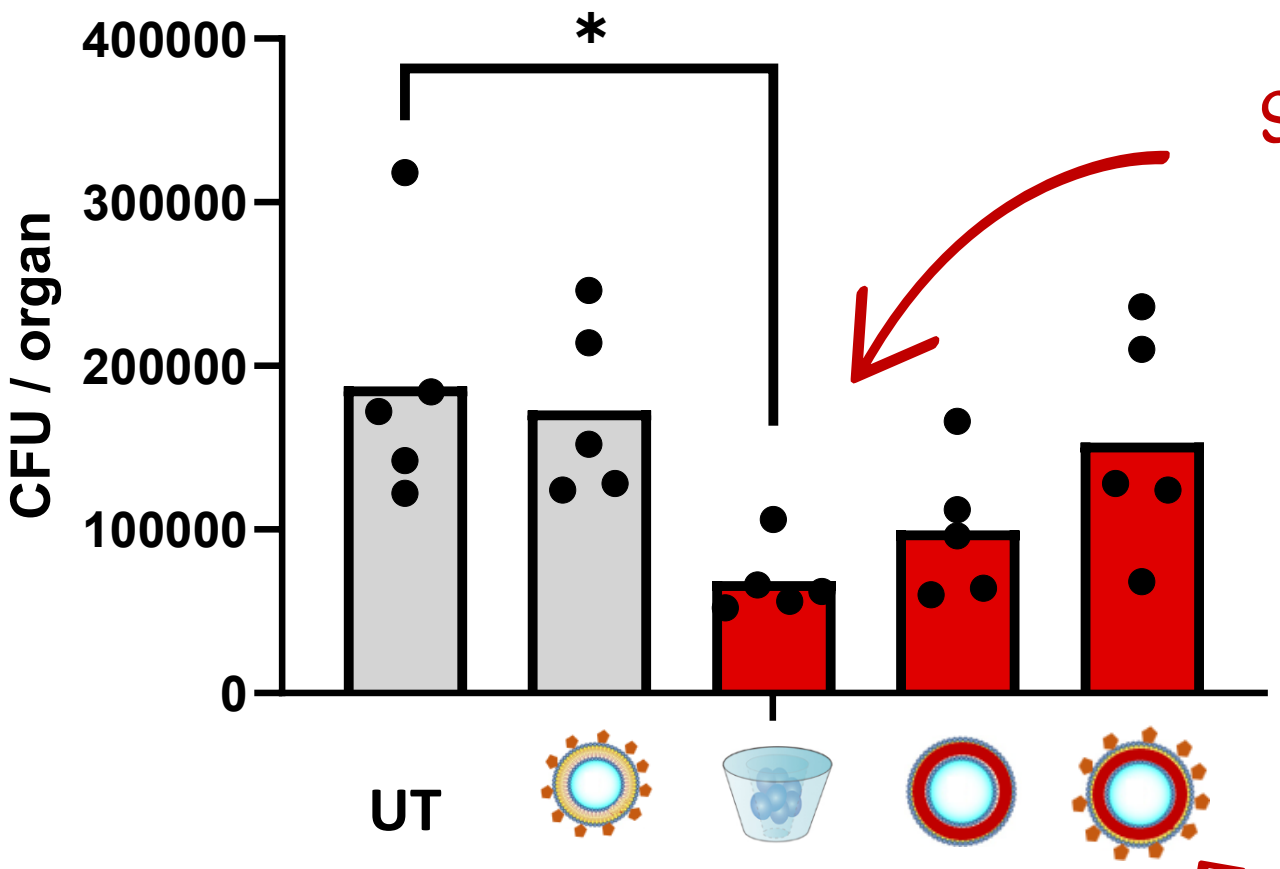
Liposomal BDQ is slightly more effective than soluble BDQ

Fucosylation did not improve efficacy

Marwitz F, ACS Infect Dis. 2024 Sep 13;10(9):3222-3232. doi: 10.1021/acsinfecdis.4c00192.

M. tuberculosis burden in the spleen

Spleen



Soluble BDQ is slightly more effective than liposomal BDQ

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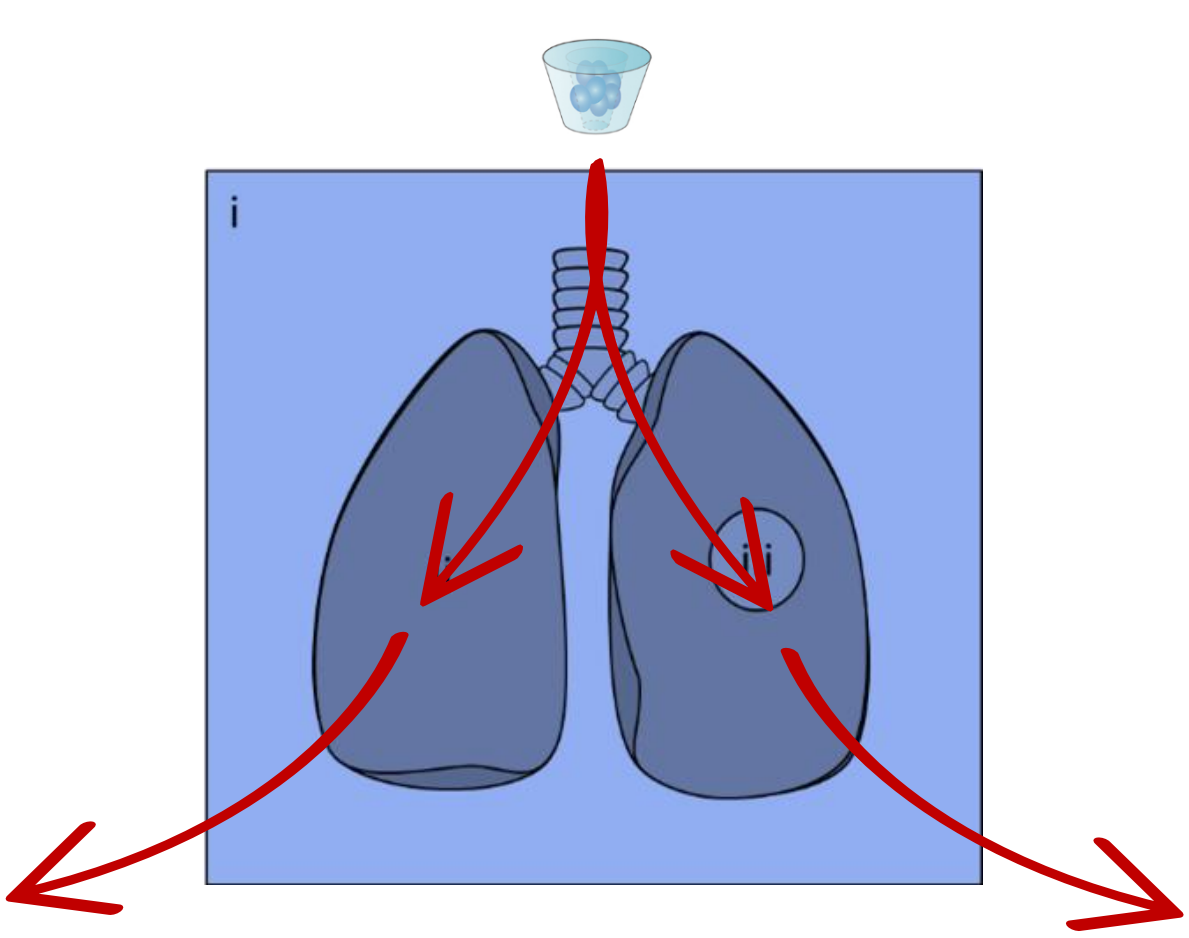
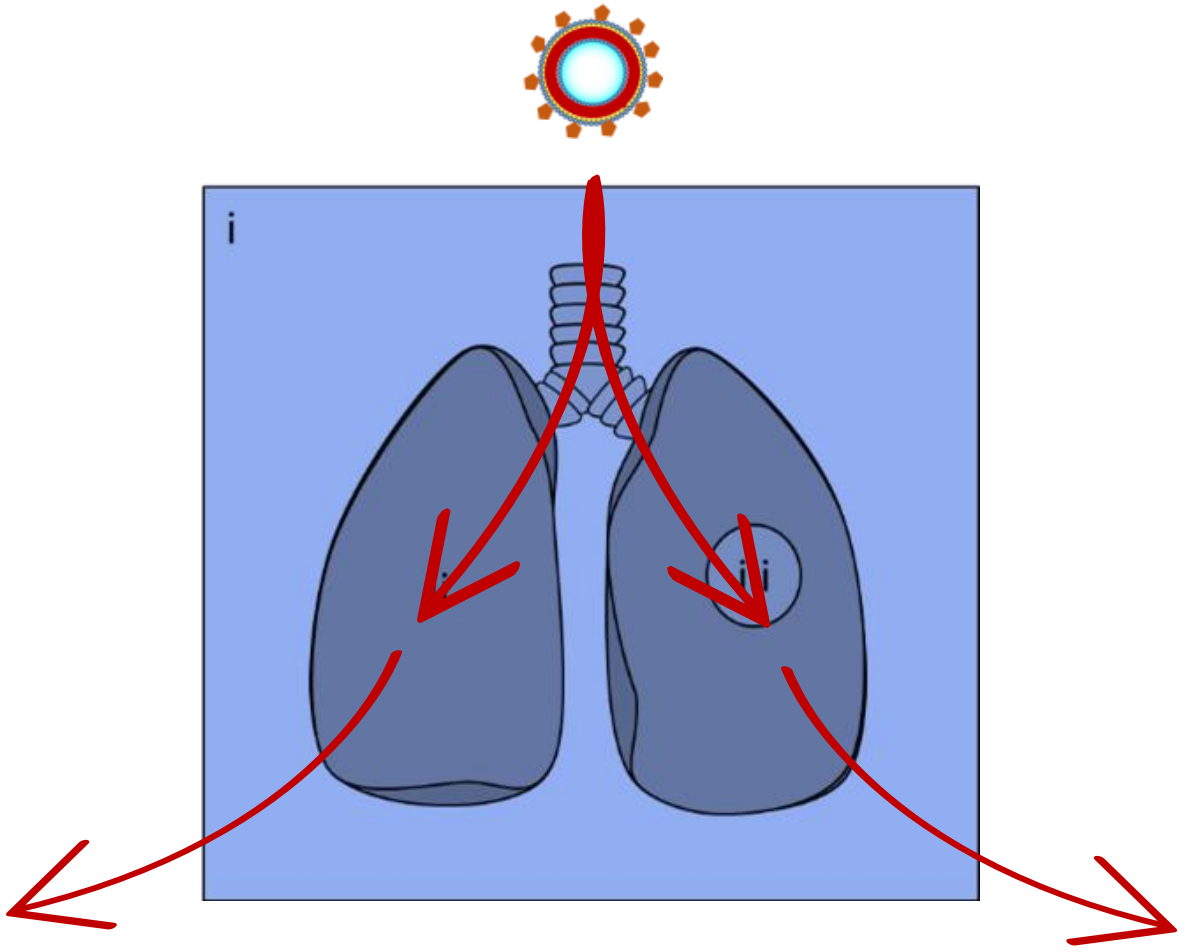
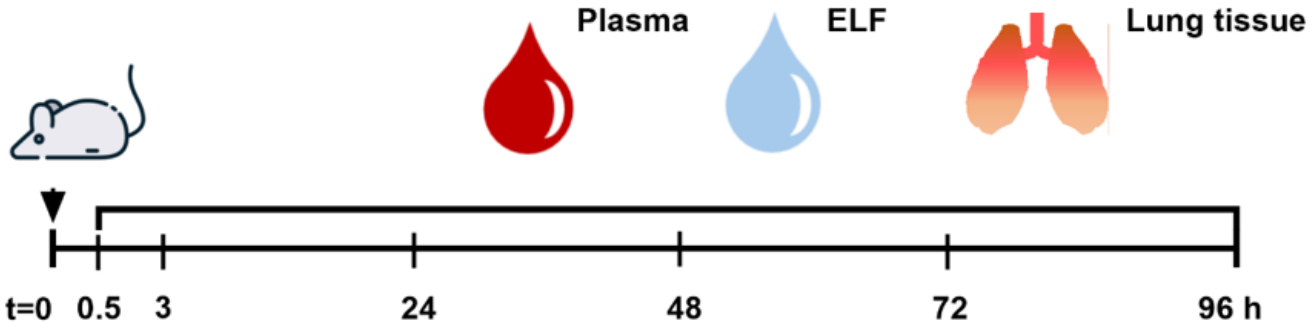
Marwitz F, ACS Infect Dis. 2024 Sep 13;10(9):3222-3232. doi: 10.1021/acsinfecdis.4c00192.

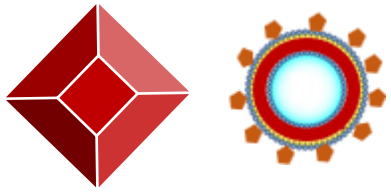
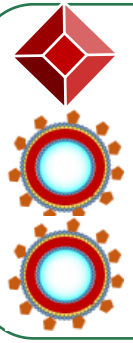
Hints of PK modulation?



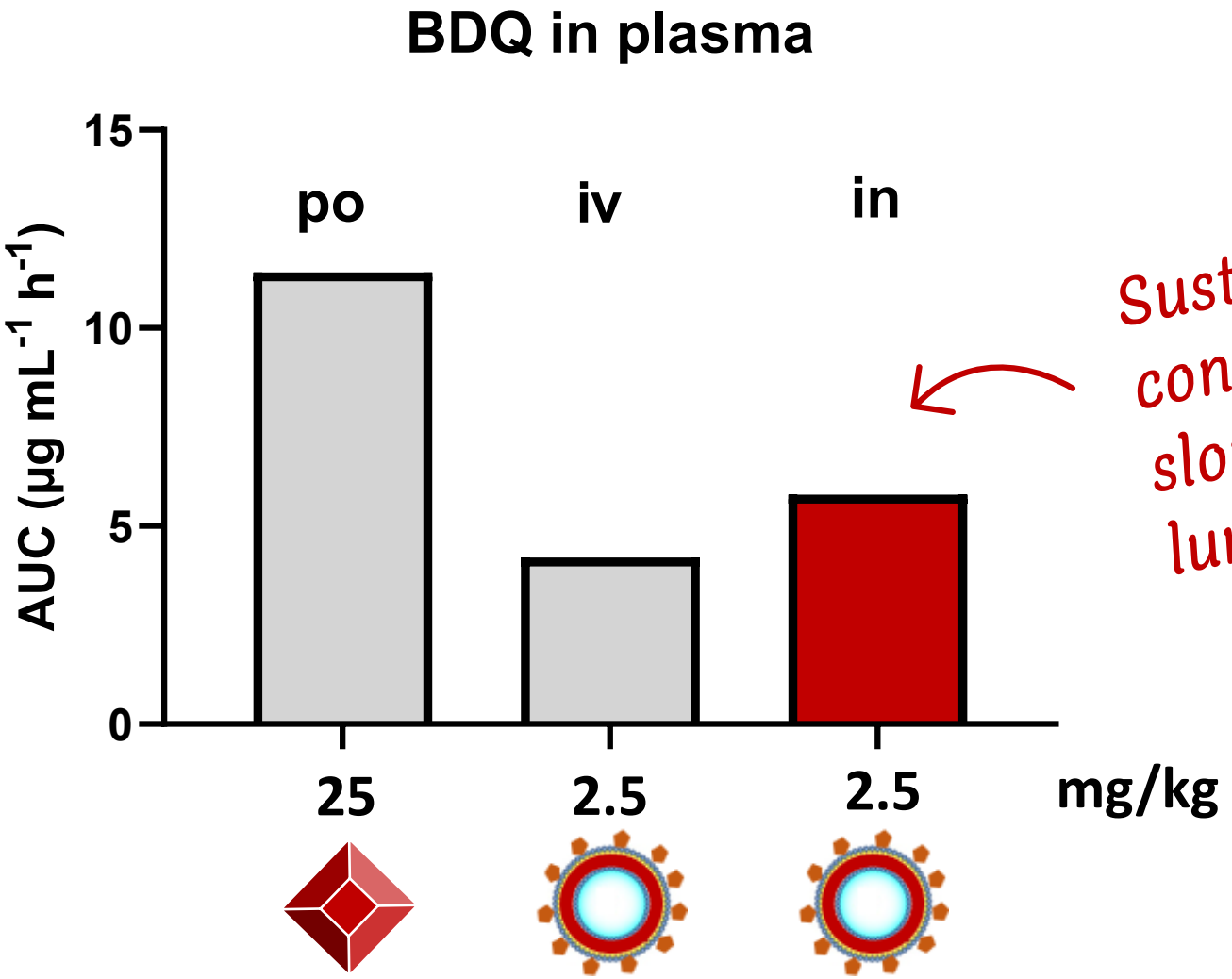


PK study comparing administration routes



Mouse model	Treatment groups (n=6)	Administration	Endpoints
Healthy Balb/c mice		 po 25 mg/kg iv 2.5 mg/kg in 2.5 mg/kg	BDQ conc in plasma, epithelial lining fluid & lung

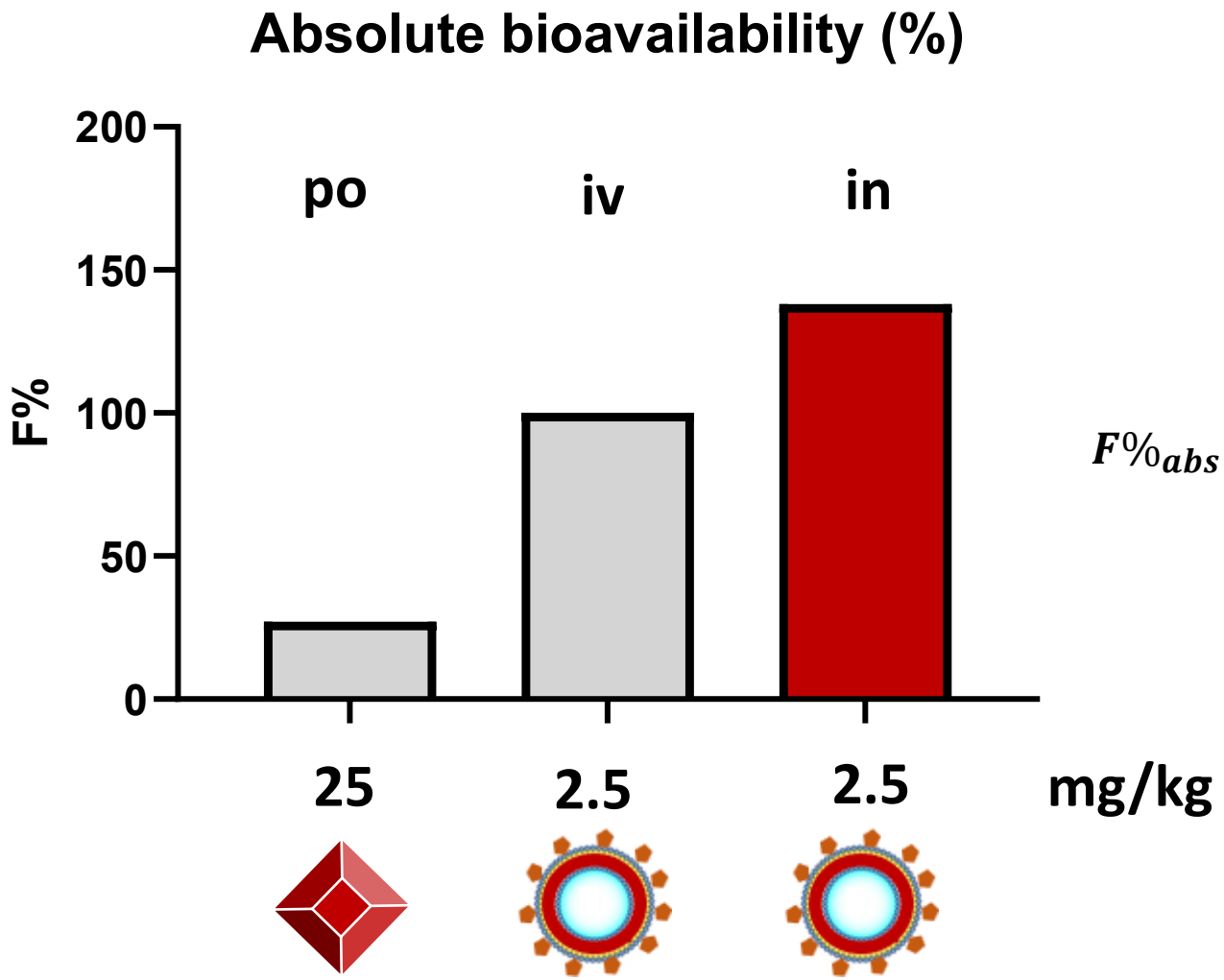
Exposure levels in plasma



Sustained BDQ plasma concentrations due to slow release from the lung

Marwitz F, ACS Infect Dis. 2024 Sep 13;10(9):3222-3232. doi: 10.1021/acsinfecdis.4c00192; Eur. Patent # EP4306130A1

Intranasal delivery improves bioavailability

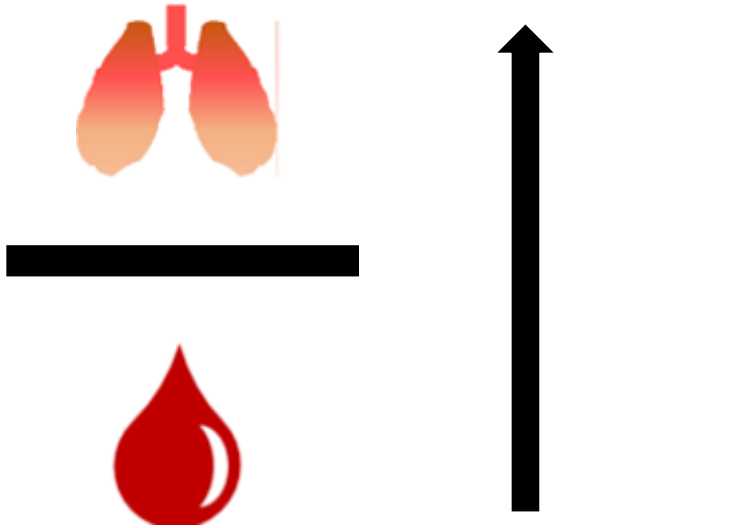


$$F\%_{abs} = 100 \cdot \frac{(AUC_{po\ or\ in} \cdot Dose_{iv})}{(AUC_{iv} \cdot Dose_{po\ or\ in})}$$

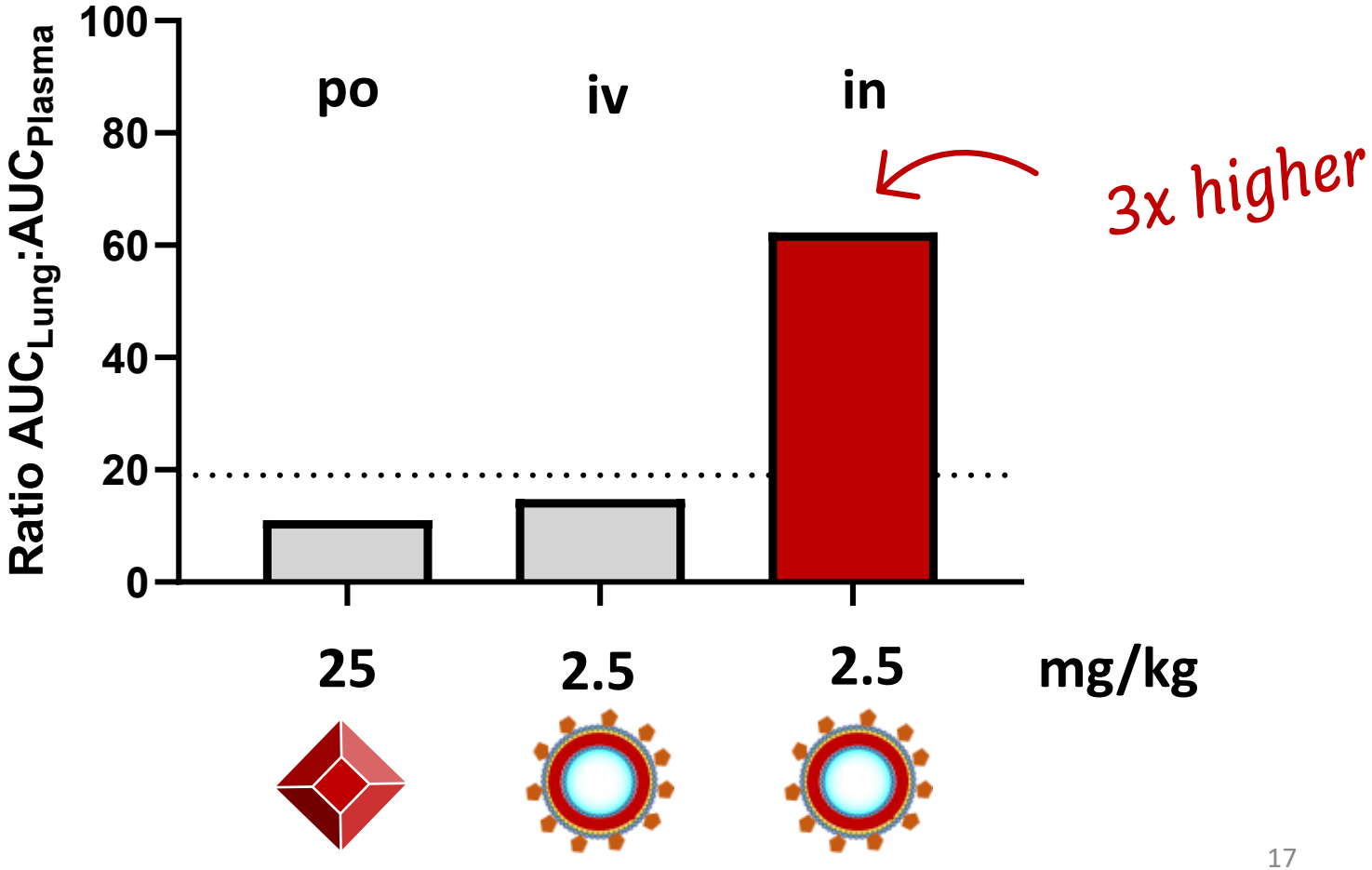
Marwitz F, ACS Infect Dis. 2024 Sep 13;10(9):3222-3232. doi: 10.1021/acsinfecdis.4c00192; Eur. Patent # EP4306130A1

Does i.n. BDQ improve lung retention?

Lung targeting effect



Lung targeting effect



Marwitz F, ACS Infect Dis. 2024 Sep 13;10(9):3222-3232. doi: 10.1021/acsinfecdis.4c00192; Eur. Patent # EP4306130A1

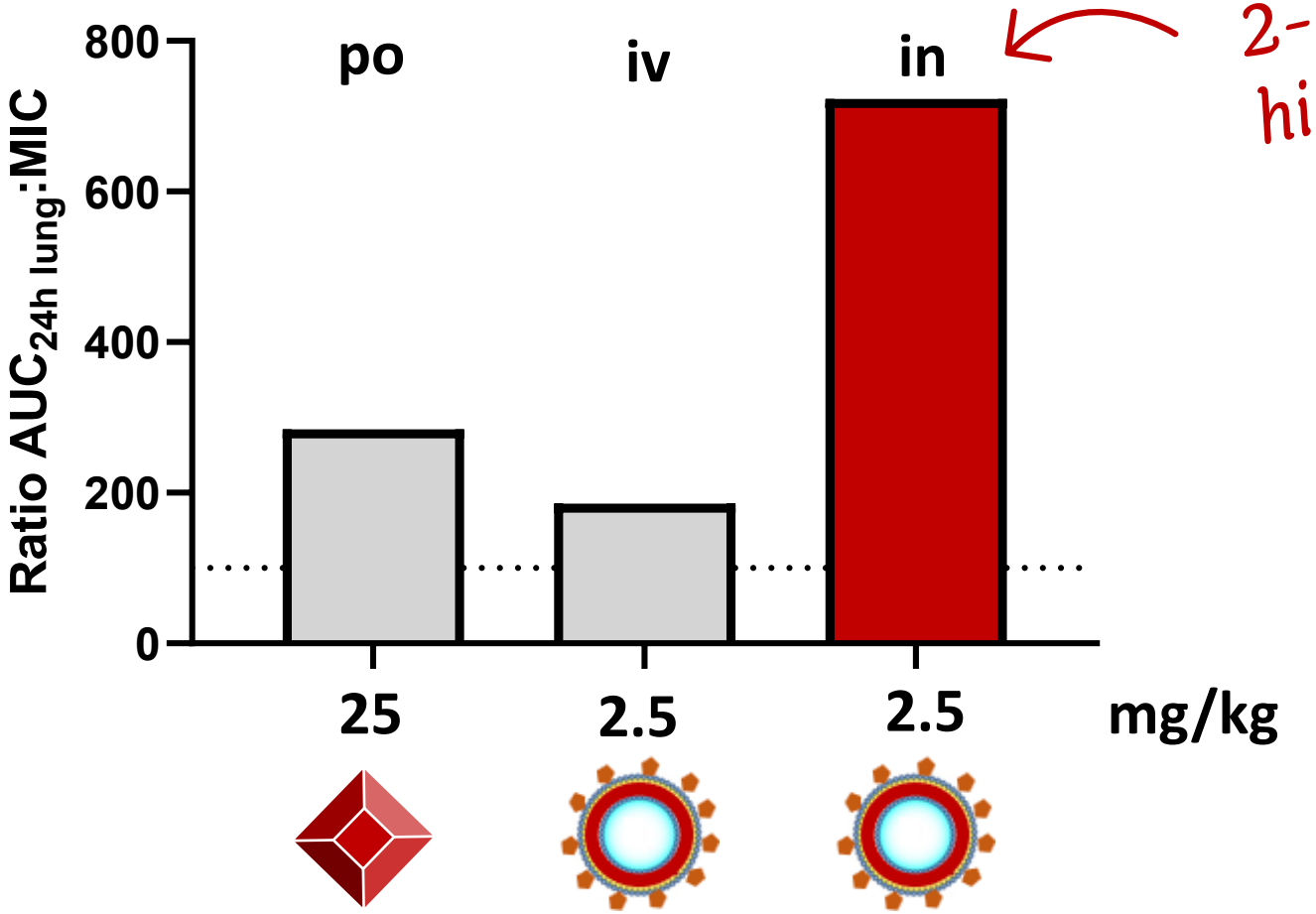
Does i.n. BDQ improve lung exposure?

Exposure in target organ (24h)

MIC

*Ideally > 100-fold**

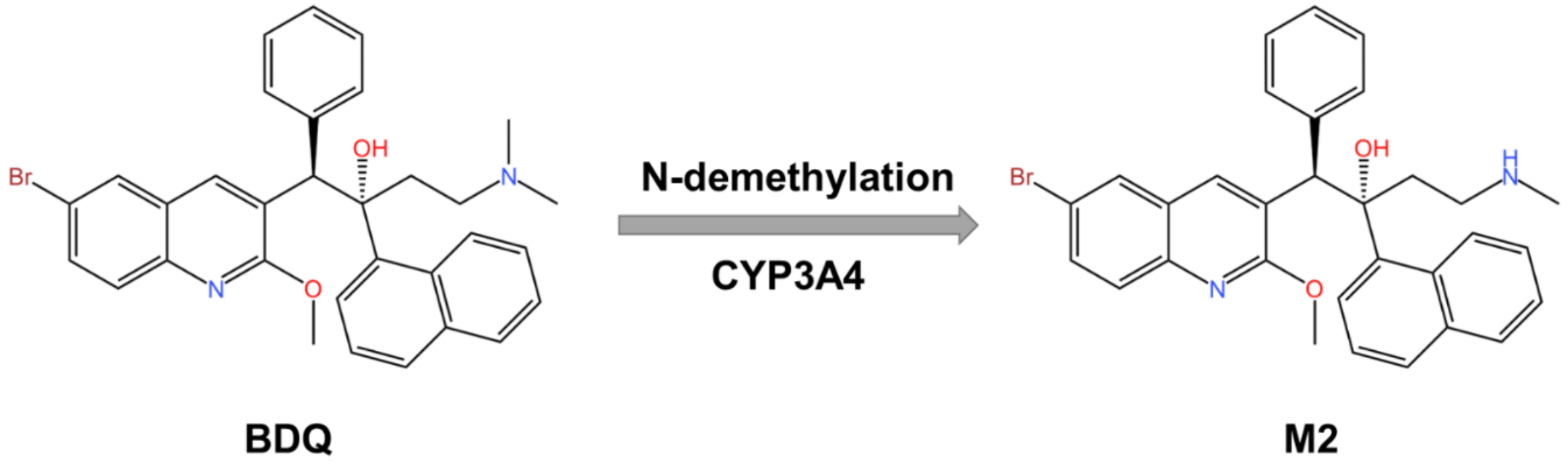
Lung AUC:MIC ratio



*Jacobs MR. Optimisation of antimicrobial therapy using pharmacokinetic and pharmacodynamic parameters. Clin Microbiol Infect. 2001 Nov;7(11):589-96.

Marwitz F, ACS Infect Dis. 2024 Sep 13;10(9):3222-3232. doi: 10.1021/acsinfecdis.4c00192; Eur. Patent # EP4306130A1

BDQ side effects: Risk of QT prolongation

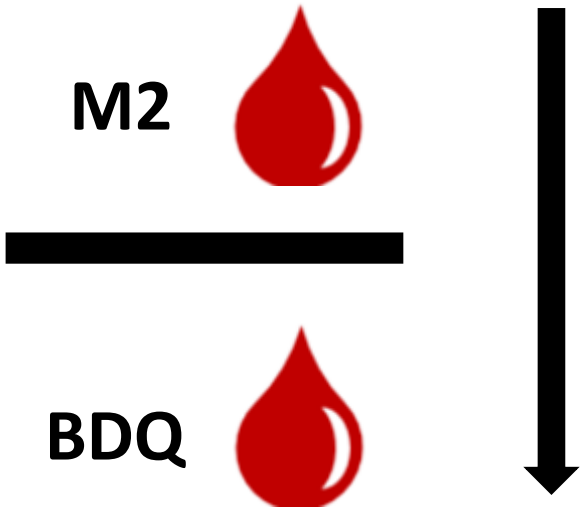


BDQ **M2**

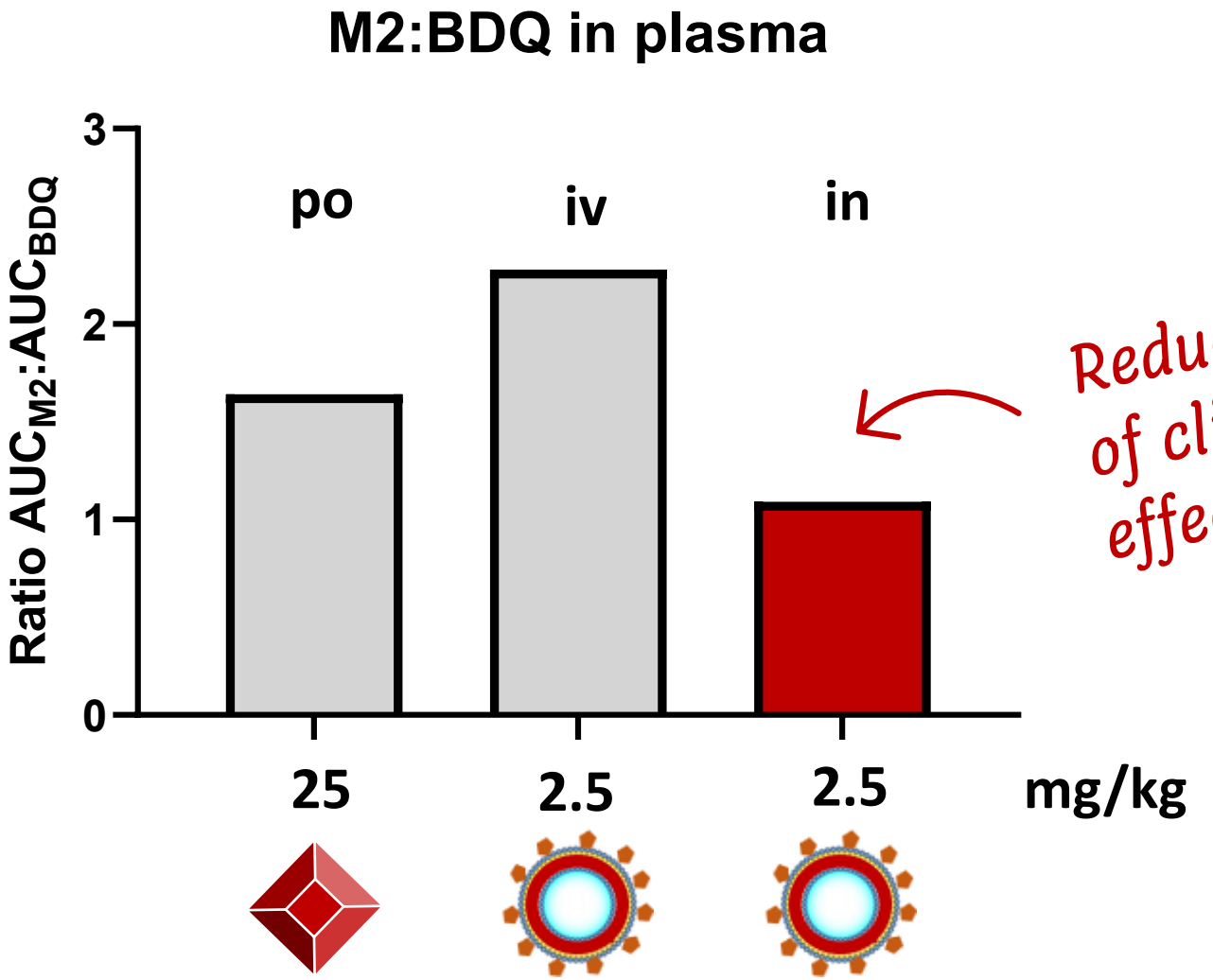
Phospholipidosis
QT prolongation

Lower plasma M2 levels: i.n. dosing

Risk of systemic side effects



Reduced side effects



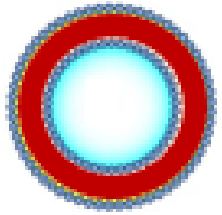
Marwitz F, ACS Infect Dis. 2024 Sep 13;10(9):3222-3232. doi: 10.1021/acsinfecdis.4c00192; Eur. Patent # EP4306130A1

Liposomal bedaquiline for inhalation

European and world patents filed!

The BDQ liposomal formulation... A fluid choice

Non-fucosylated liposomes

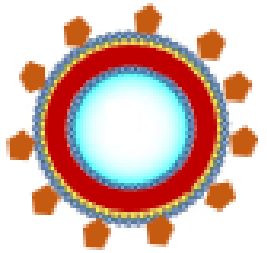


C14 lipids

- DMPC:DMPG (2:1) liposomal composition
- Tm ~23°C (without drug)
- Lipid:BDQ mol ratio = ~15:1

Quite low Tm

Fucosylated liposomes



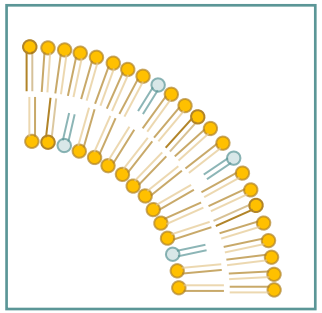
- DMPC:DMPG (2:1) liposomal composition
- 8 mol% cholesterol-fucose conjugate
- Lipid:BDQ mol ratio = ~15:1

Tm of drug-loaded, fucosylated systems likely even lower

Unintentionally reminiscent of the fluidosome concept

Fluidosomes: Beaulac et al, 1996

Low fluidity

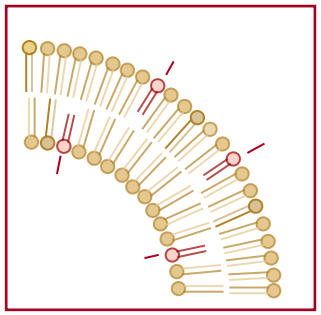


mol %

DMPC (C14): 1
DSPC (C18): 15

Tm: 42.0°C

High fluidity



mol %

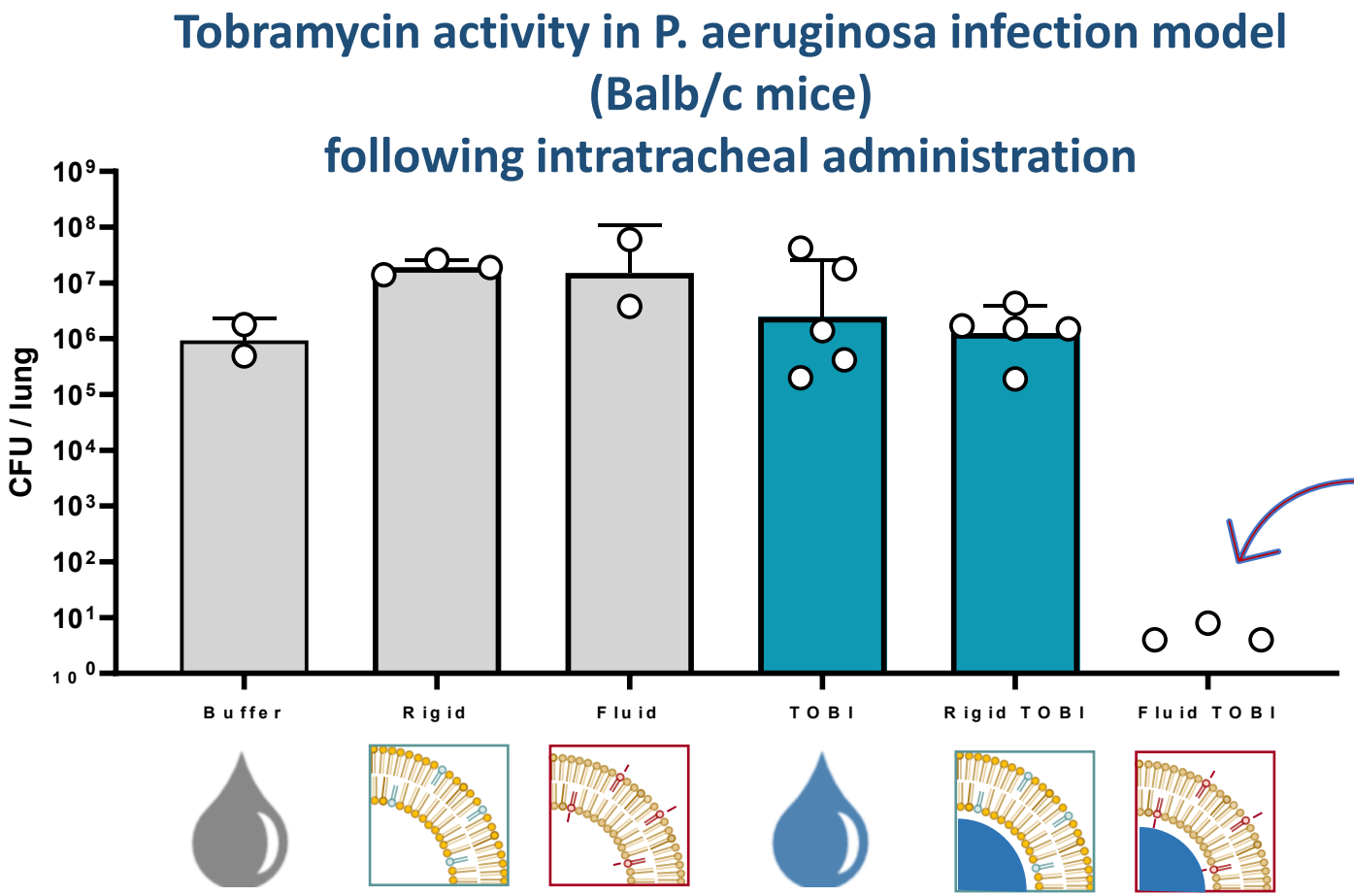
DMPG (C14): 1
DPPC (C16): 10

Tm: 29.5°C

Beaulac et al ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 1996, p. 665–669

In vivo proof-of-concept: Fluidosomes

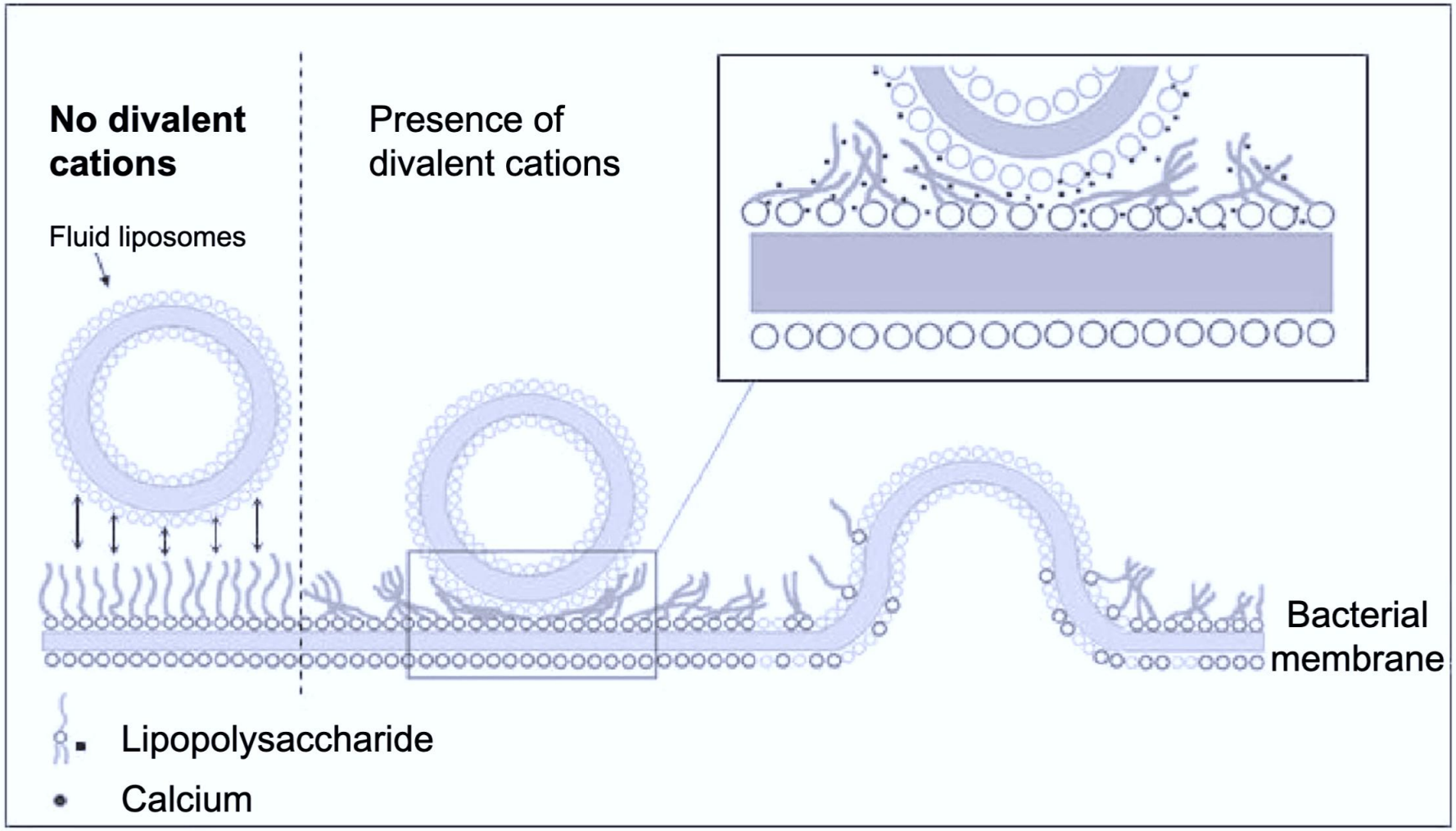
Fluidosomes: Beaulac et al, 1996



Reduction in CFU 5-6 magnitudes of order!

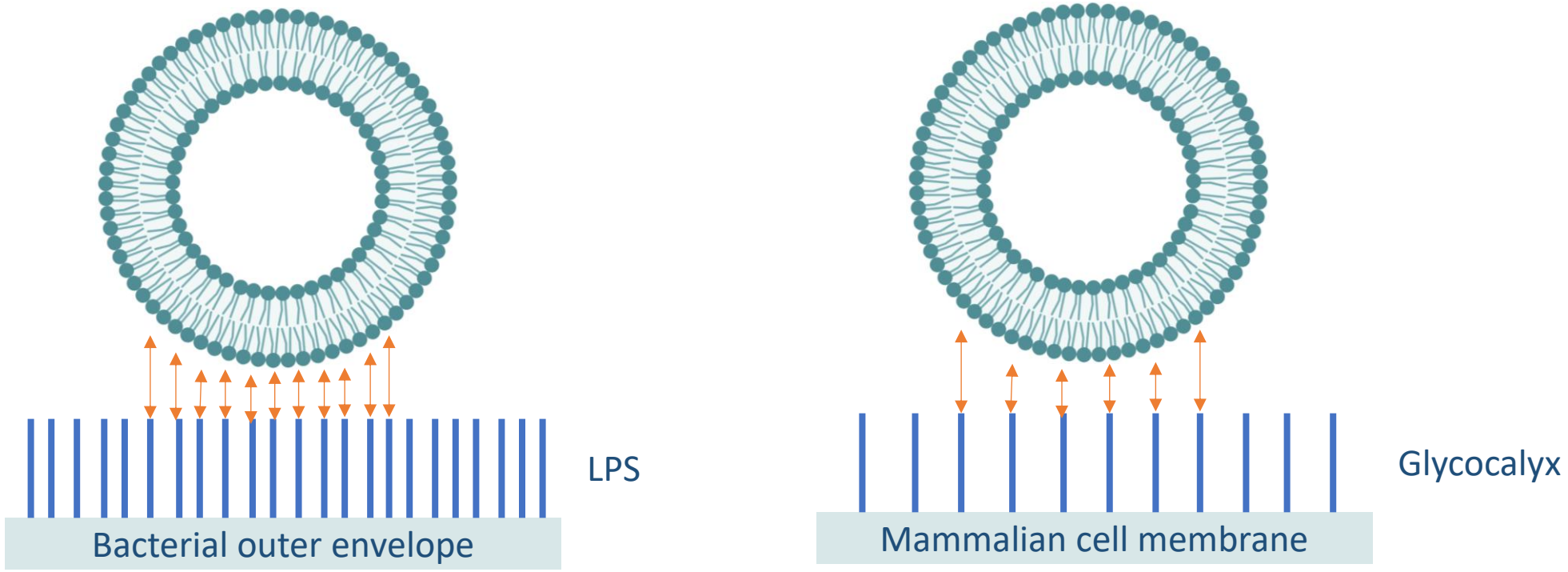
Beaulac et al ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 1996, p. 665–669

Hypothesized mechanism: Membrane fusion



Wang, et al 2016

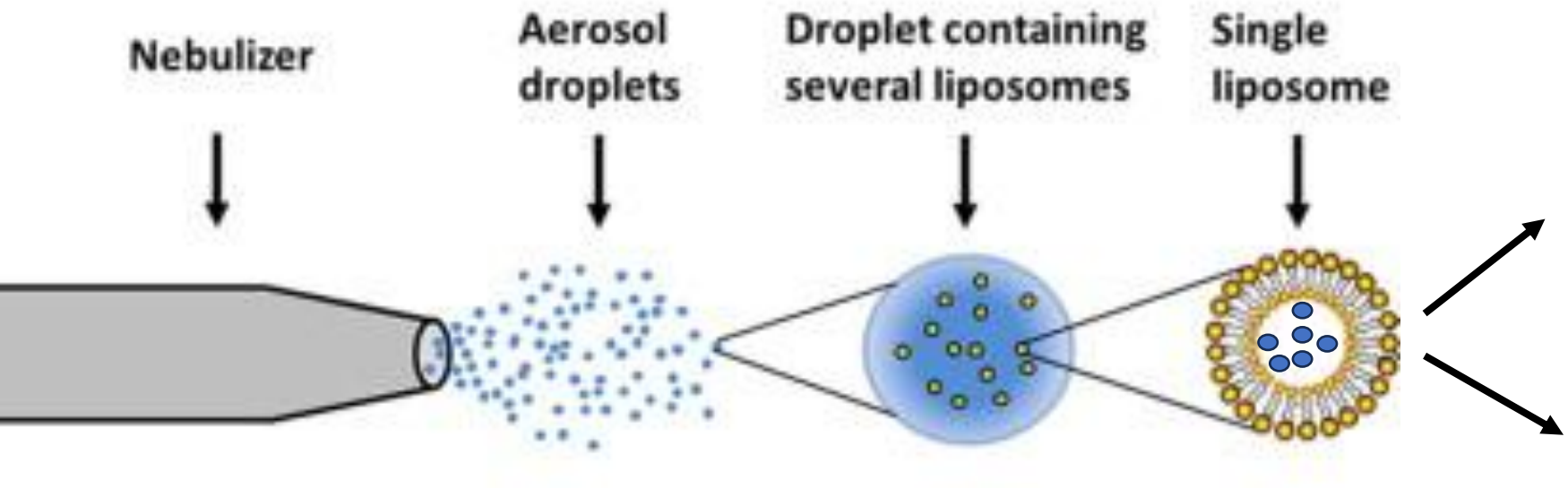
Hypothesized selectivity: Mechanism



Wang, et al 2016

Why weren't fluidosomes commercialized?

Hydrophilic drug leakage following nebulization



Ultradeformable liposomes

> 70% leakage

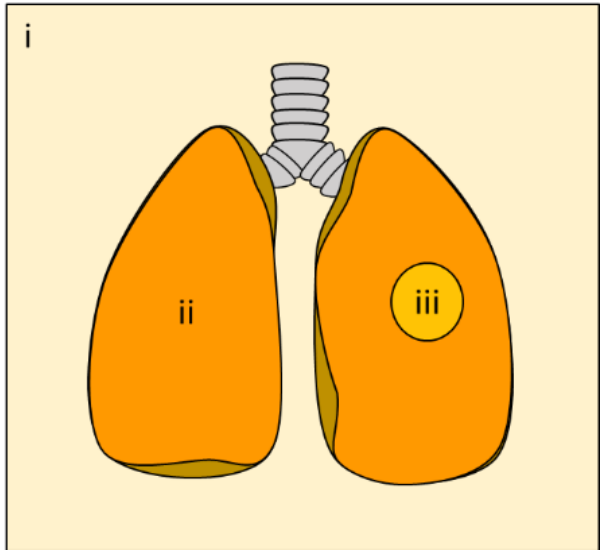
Conventional liposomes

< 30% leakage

Elhissi et al, 2012, Int J Pharm, 436, 519-526.

Many anti-infectives are hydrophilic, but not all…

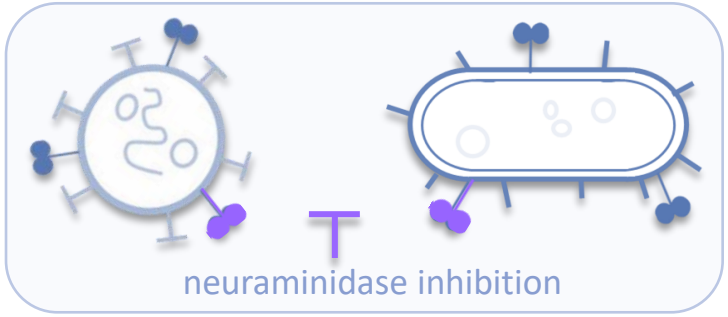
Poorly soluble anti-infectives for inhalation: The sequel



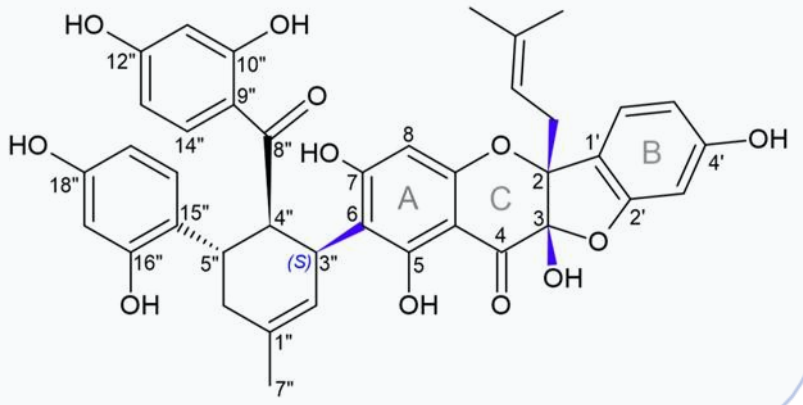
Sanggenon C & D

stereoisomeric natural products

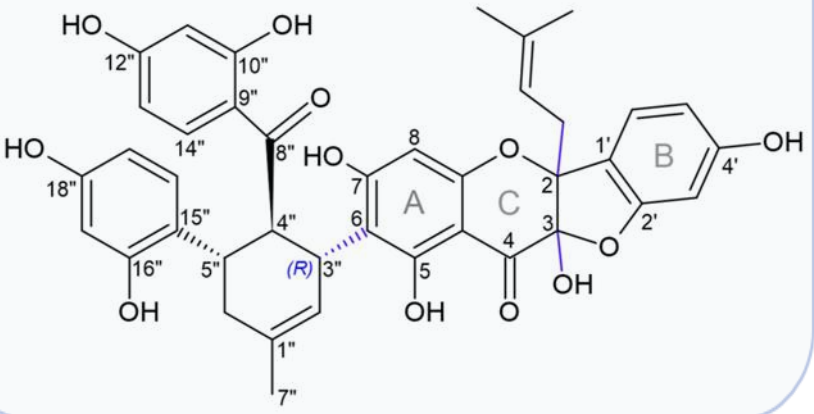
- prenylated flavonoids
- stereoisomers differing at C3’’
- Antiviral & antibacterial activity
  - dual neuraminidase inhibition



Sanggenon C

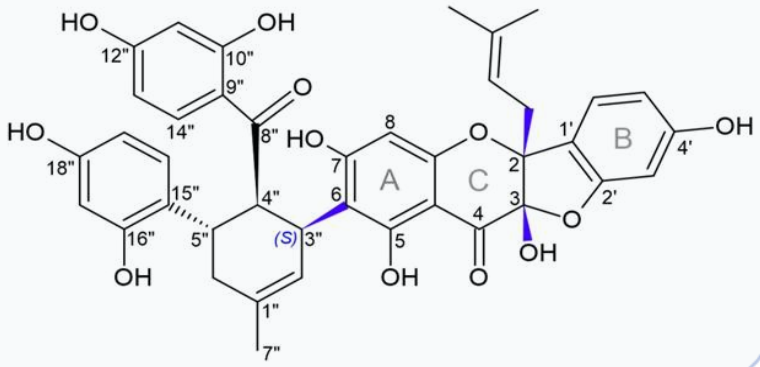


Sanggenon D



Sanggenon stereoisomers are markedly different

Sanggenon C



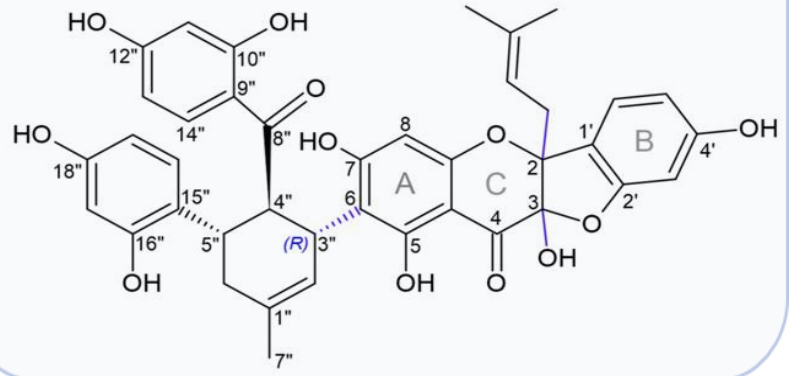
Moderately low solubility

50 µg/mL

Log P

3.48

Sanggenon D



Moderate solubility

500 µg/mL

Log P

2.92

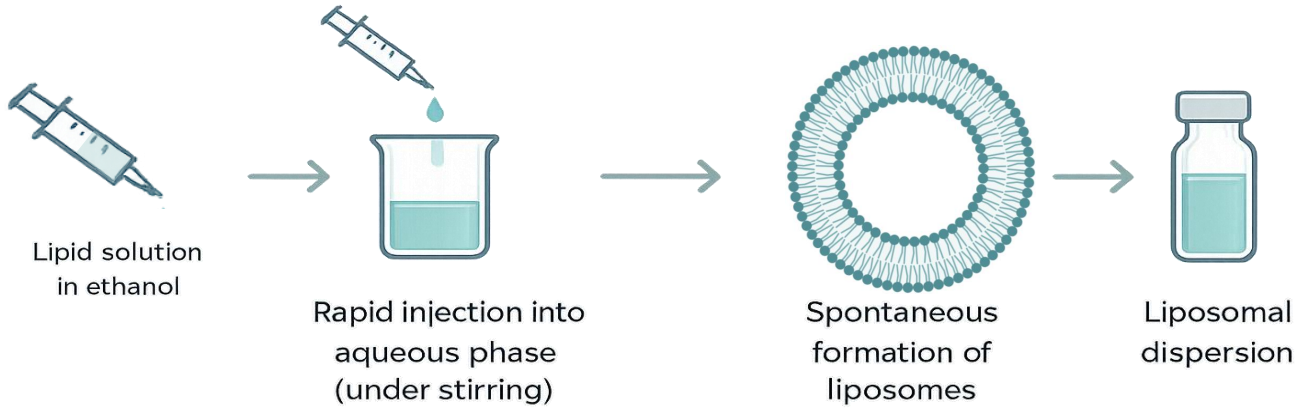
oral BA: not measurable

Schwarzinger J, et al. Int J Pharm X. 2024 Aug 5;8:100272. doi: 10.1016/j.ijpx.2024.100272.

Hey…if liposomes worked for bedaquline, then why not?

overcoming solubility limitations

ETHANOL INJECTION



COMPOSITION

- DMPC:DMPG (2:1)
- Lipid:sanggenon (5:1)
- Adjusted volume to achieve 3.5 to 4 mg/mL drug
- Vehicle: sterile 0.9% NaCl

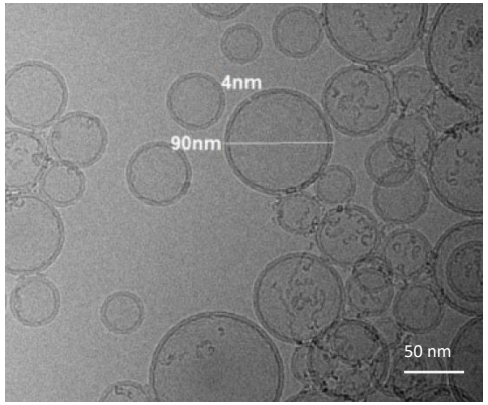
Schwarzinger J, Eur J Pharm Sci. 2025 Dec 1;215:107361.

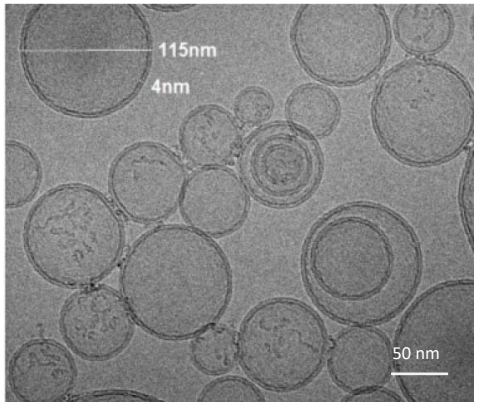
It was surprisingly easy…

Parameter	SGC-Lip	SGD-Lip	Interpretation
size	98	117	suitable nm-sized vesicles
PDI	0.19	0.21	narrow size distribution
drug loading (mg/mL)	3.56	3.78	high drug loading
EE	99%	96%	efficient incorporation
size stability	✓	✓	stable over 8 weeks and after nebulisation

Representative Cryo-TEM images

SGC





SGD

Schwarzinger J, Eur J Pharm Sci. 2025 Dec 1;215:107361.

Success friends!

overcame solubility limitations

SGC

Aqueous solubility
~50 µg/mL

drug loading
~3560 µg/mL

70x

SGD

Aqueous solubility
~500 µg/mL

drug loading
~3780 µg/mL

7x

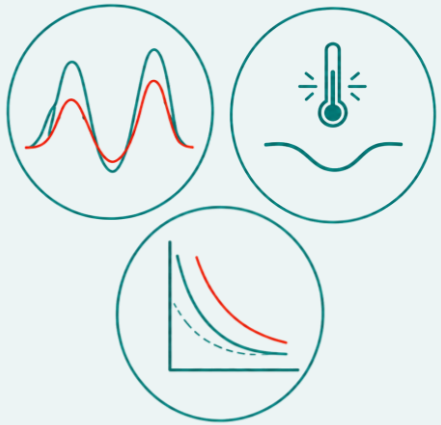
Sanggenons are very happy in the lipid bilayer

Fluid DMPC:DMPG liposomes can accommodate a high sanggenon content

biophysical methods

SAXS

DSC



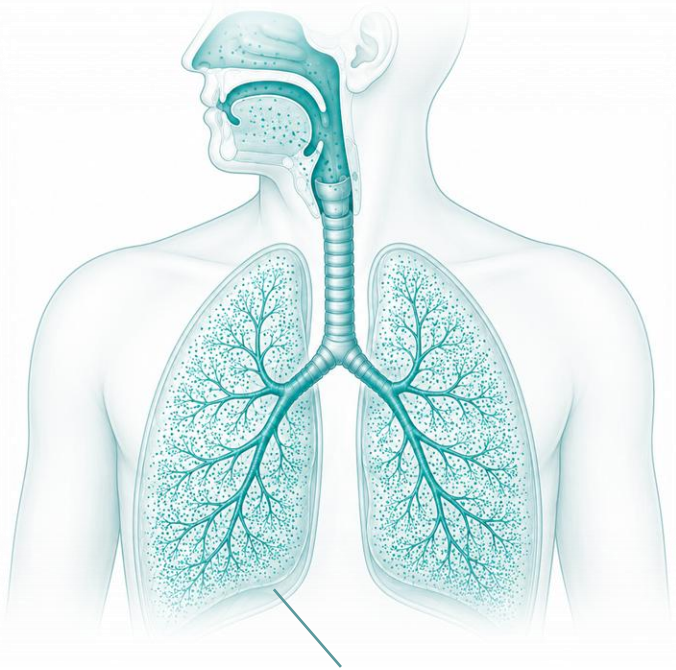
Langmuir monolayer studies

Schwarzinger J, Eur J Pharm Sci. 2025 Dec 1;215:107361.

- strong drug–lipid interactions (planarity?)
- fluidizing effect on lipids
- stereoisomeric differences visible, but less pronounced in final liposomes
- higher drug loading potential suggested

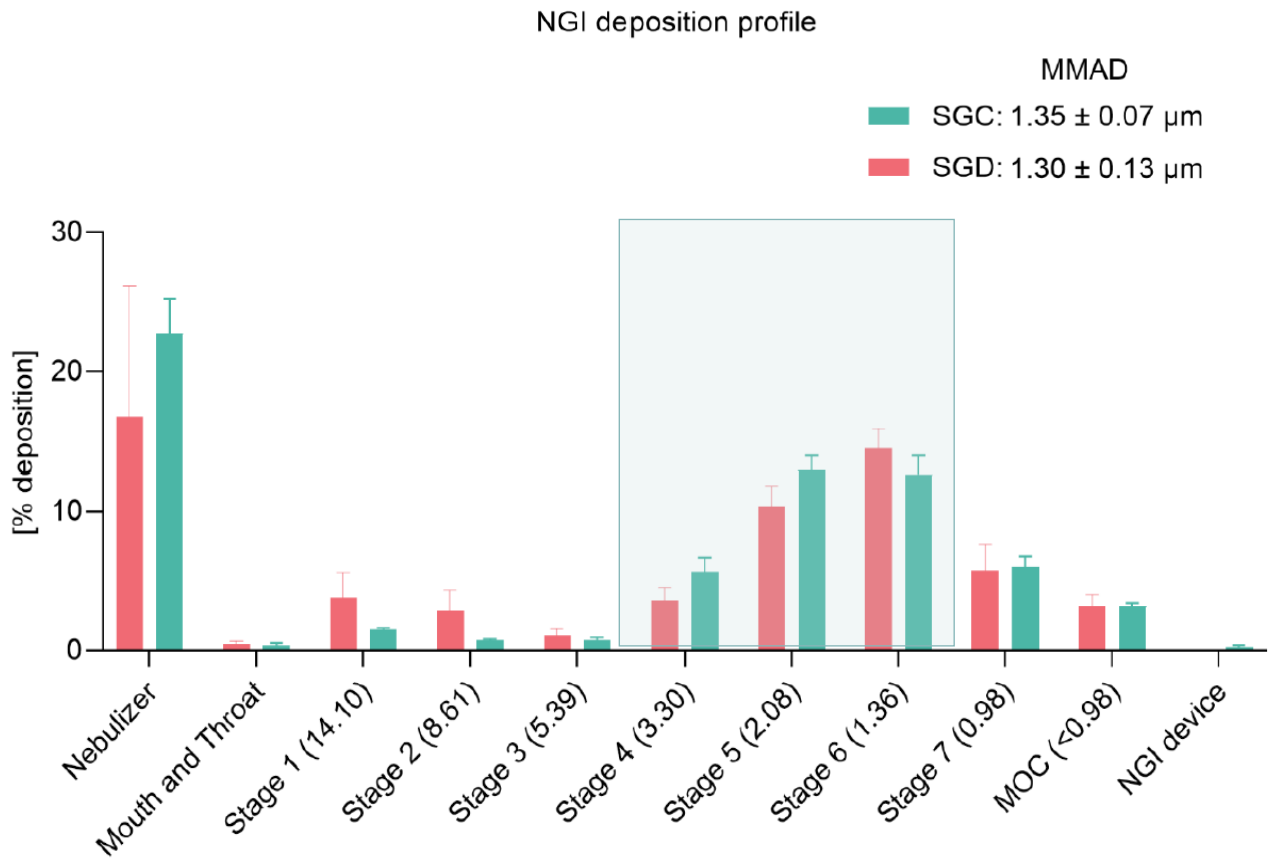
Nebulization is no problem!

aerosol performance



1-5 µm

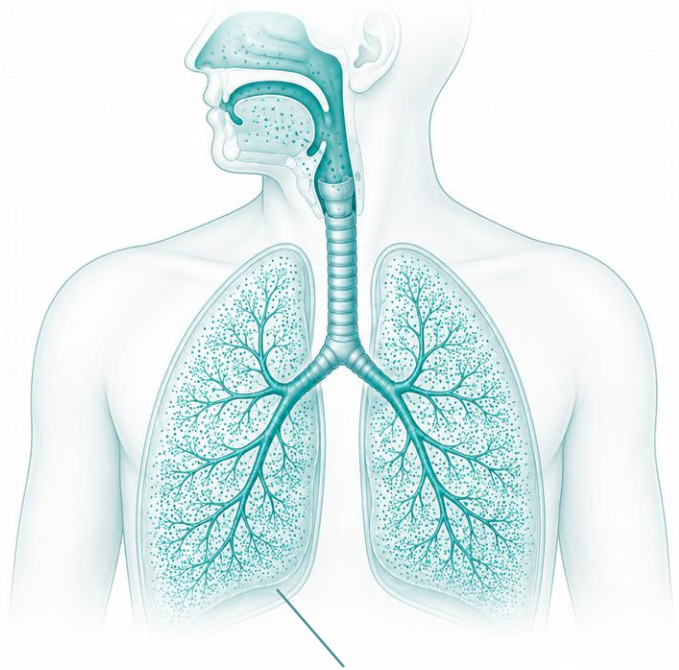
Homogeneous lung deposition, extending into the deep lungs



both formulations generated respirable aerosols suitable for pulmonary delivery

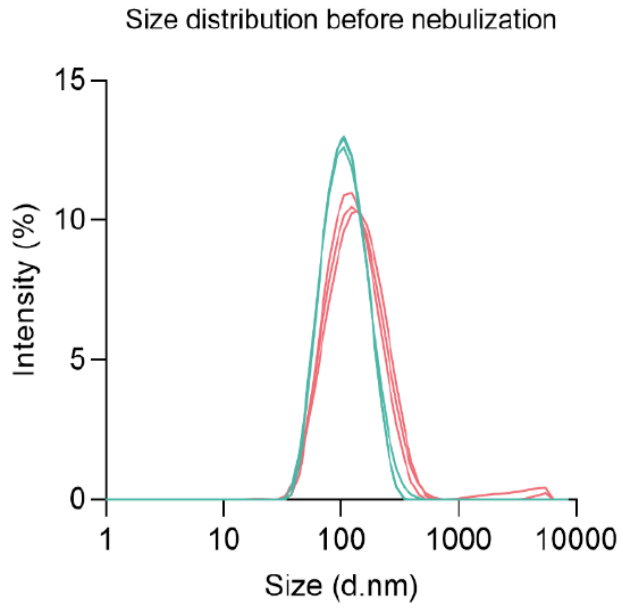
Nebulization is no problem!

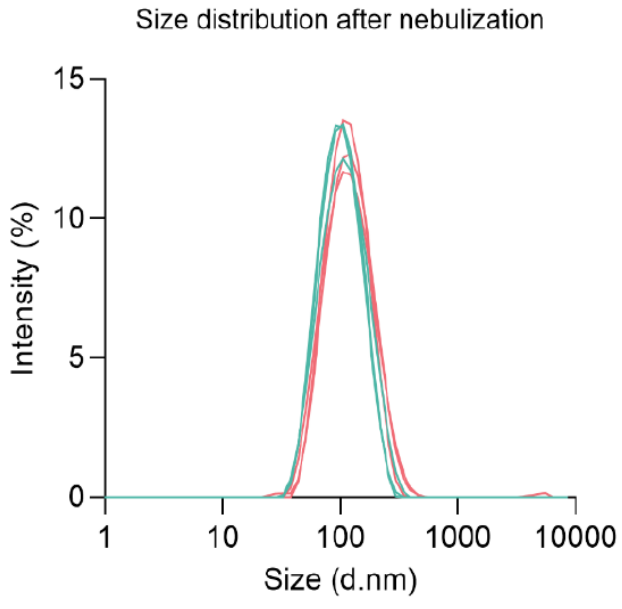
aerosol performance



1-5 µm

Homogeneous lung deposition, extending into the deep lungs





both formulations generated respirable aerosols suitable for pulmonary delivery

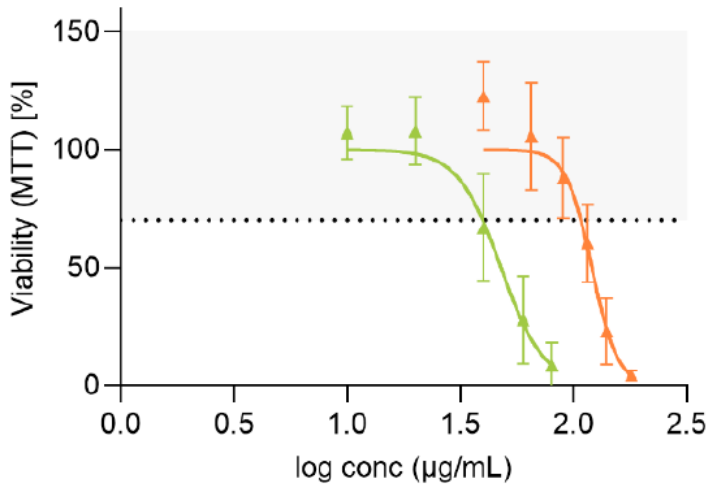
Fluid liposomes do not appear to fuse with mammalian cell membranes

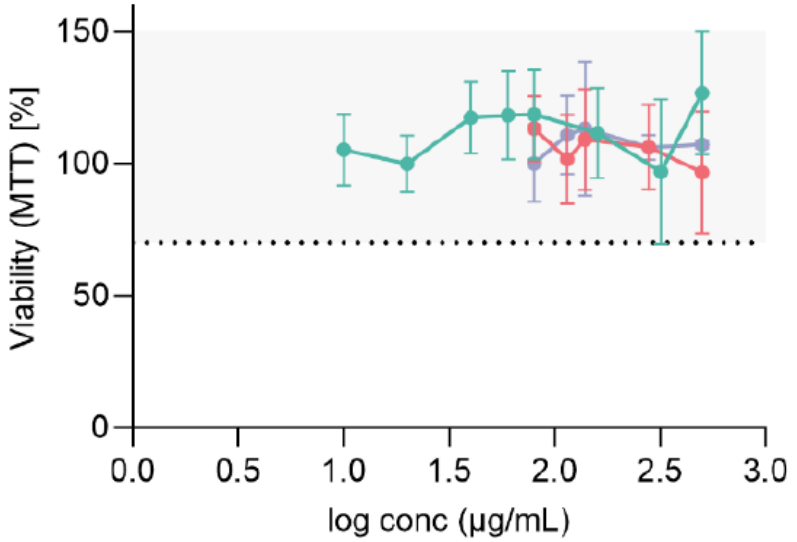
Fluid liposomes protect against sanggenon-induced cytotoxicity

pure compounds

liposomes

MTT





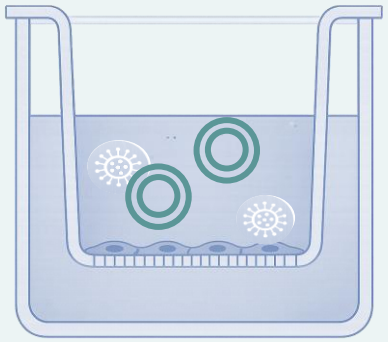
Blank-Lip SGC SGD SGC-Lip SGD-Lip

Schwarzinger J, Eur J Pharm Sci. 2025 Dec 1;215:107361.

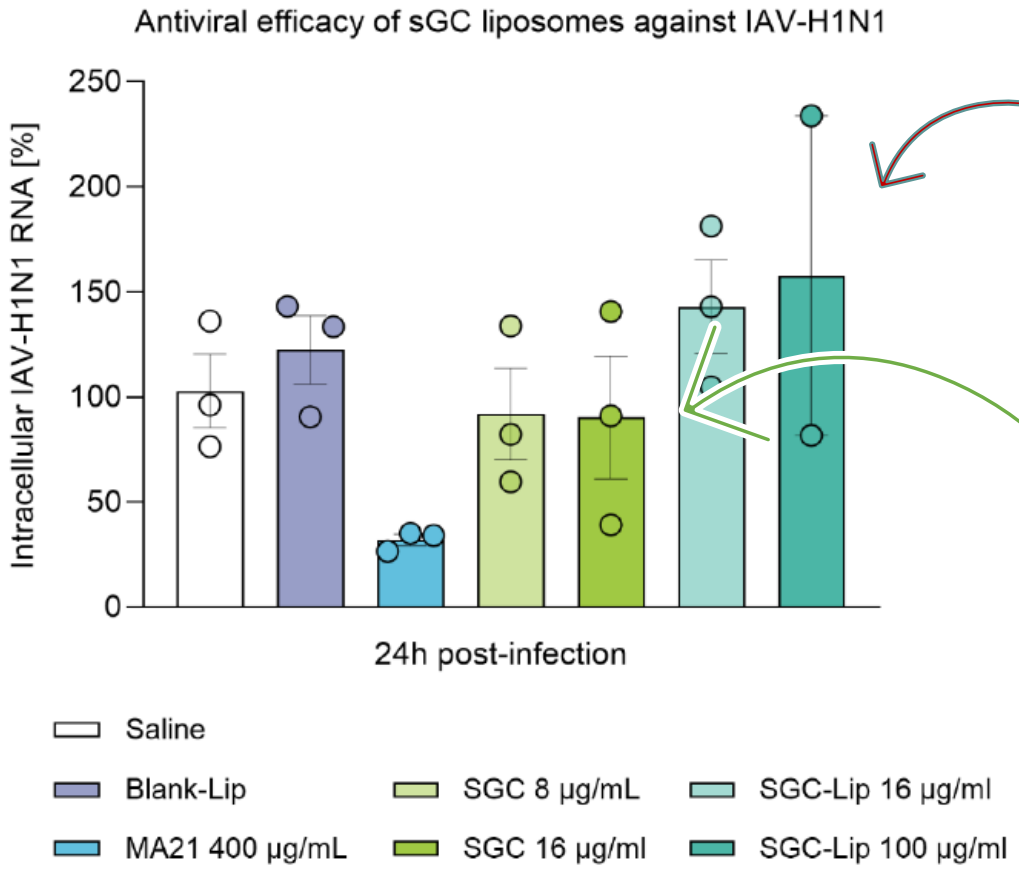
First attempt at efficacy studies

Can SGC-loaded liposomes reduce intracellular viral RNA load?

Influenza A infection model



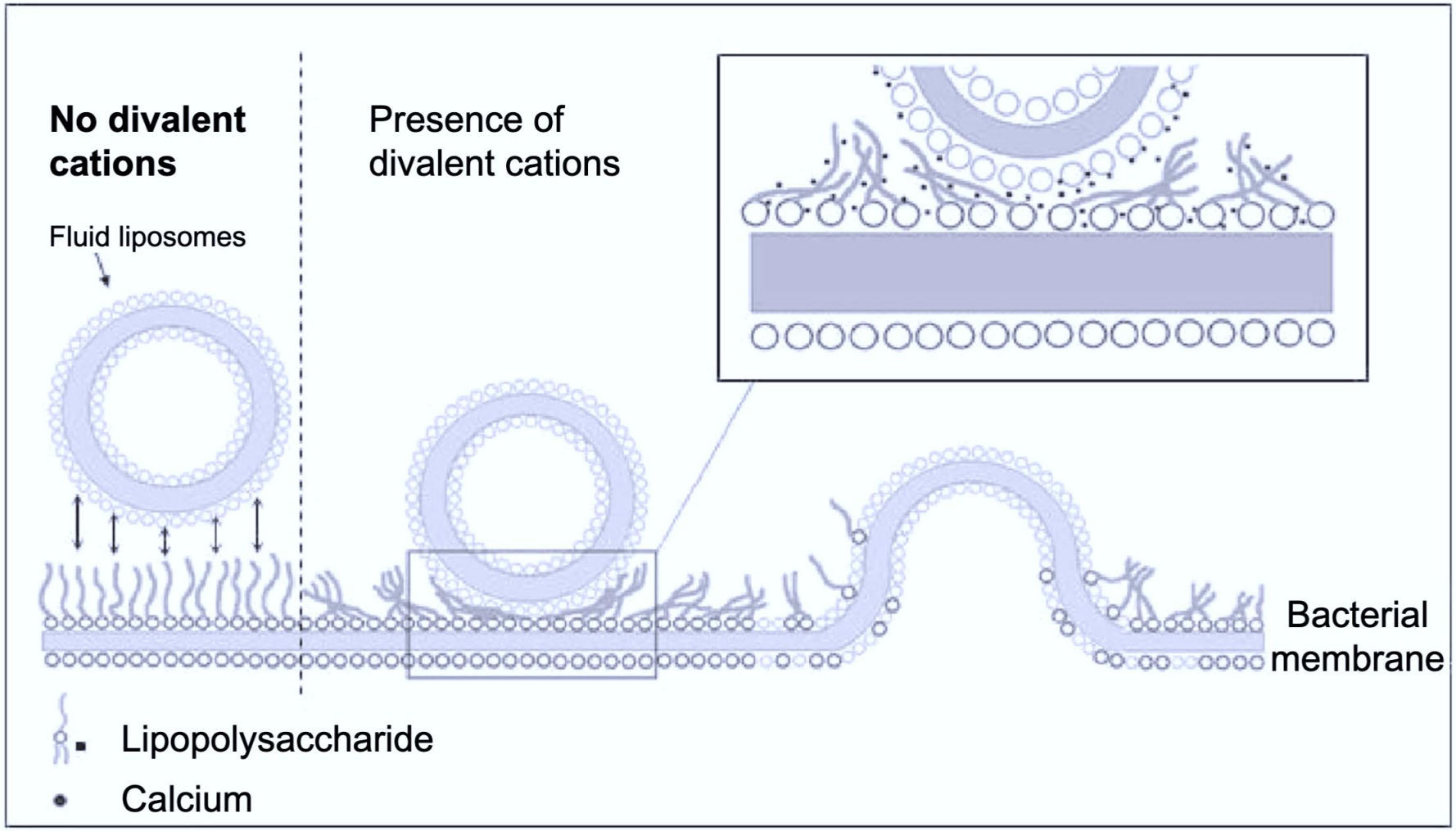
HBEC3-KT cells



No effect of liposomal SGC at two concentrations

But also no effect of an SGC solution at two concentrations supposedly > MIC

Are fluidosomes specifically active against bacteria?

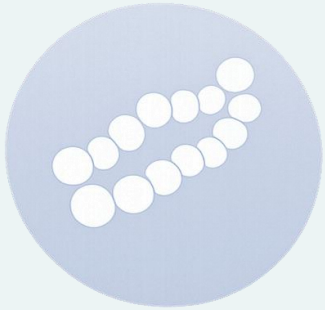


Wang, et al 2016

Future studies planned...

Now that we have approval for Biosafety Level 2 studies...

S. pneumoniae model



Planktonic and biofilm models

Efficacy study	SGC	SGD
S. pneumoniae (ATCC 33400), MIC_{90} [117]	2.7 ± 0.4 µg/mL	8.7 ± 3.5 µg/mL
S. pneumoniae (ATCC 33400), $MBIC_{90}$ [117]	1.1 ± 0.4 µg/mL	5.9 ± 0.2 µg/mL
IC_{50} values of influenza A viral replication in MDCK cells [117]	8.3 ± 0.7 µg/mL	no activity
IC_{50} values of SARS-CoV-2 viral replication in Calu-3 cells [115]	4.6 µM	18.5 µM
S. aureus (ATCC 6538), MIC [120]	70.6 µmol/L	17.6 µmol/L
S. aureus (MRSA, ATCC 43300), MIC [122]	3.16 µM	10 µM
E. faecalis (ATCC 29212), MIC [121]	3.125 µM	12.5 µM
E. faecalis (vancomycin-resistant ATCC 51575), MIC [121]	3.125 µM	12.5 µM
E. faecium (ATCC 35667), MIC [121]	3.125 µM	25 µM
E. faecium (vancomycin-resistant ATCC 70021), MIC [121]	3.125 µM	12.5 µM

Let's revisit fluid liposomes for inhalation of poorly soluble anti-infectives

①	②	③	④
High dose lipophilic APIs	Lung retention	Fusogenic properties with bacteria	Stability
⇩	⇩	⇩	⇩
Accumulation + non-specific inflammation	Fast clearance of lipophilic APIs	Improved drug efficacy	Can be nebulized without drug loss

Acknowledgements

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- Richard D. Harvey

NPQ study:

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- Leonie Wurster
- Richard D. Harvey

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