Tetraether lipid (and CPP-modified) liposomes for oral peptide delivery

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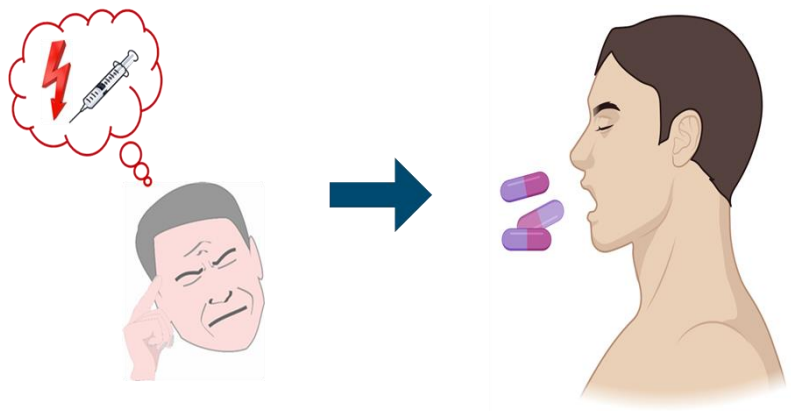
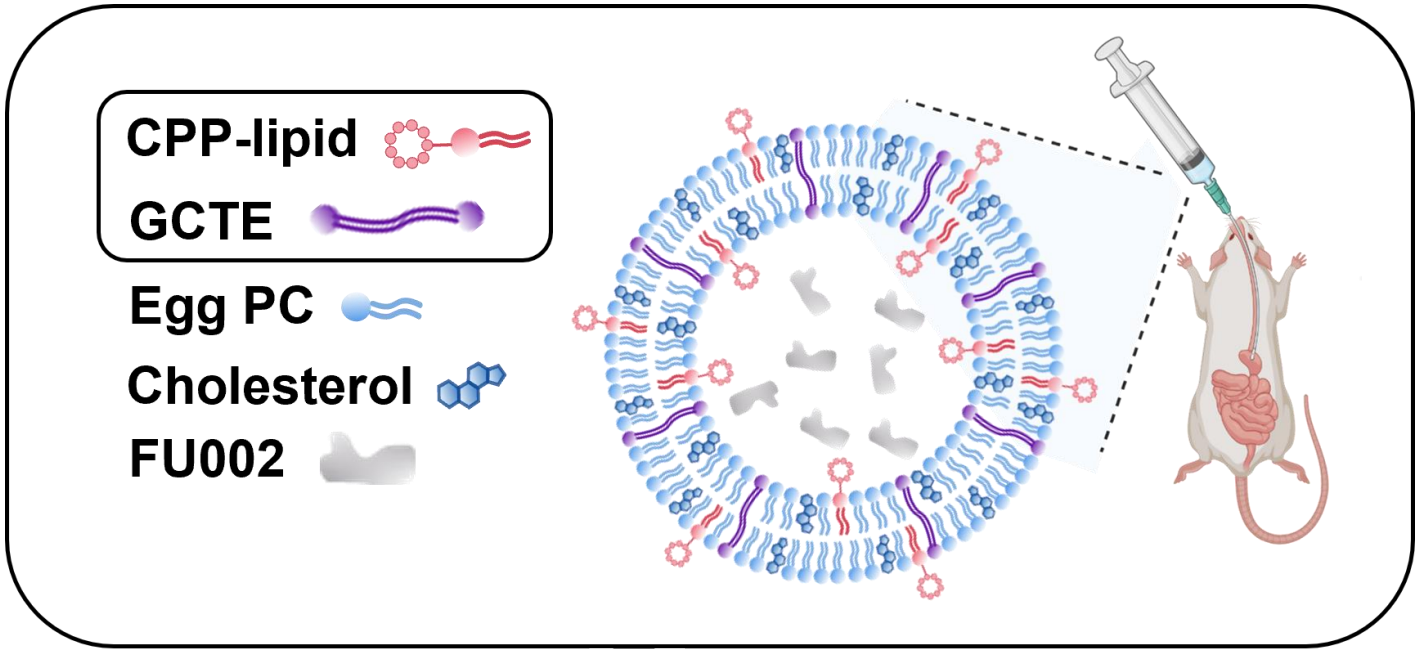
09.09.2024

Repeated (daily) injections

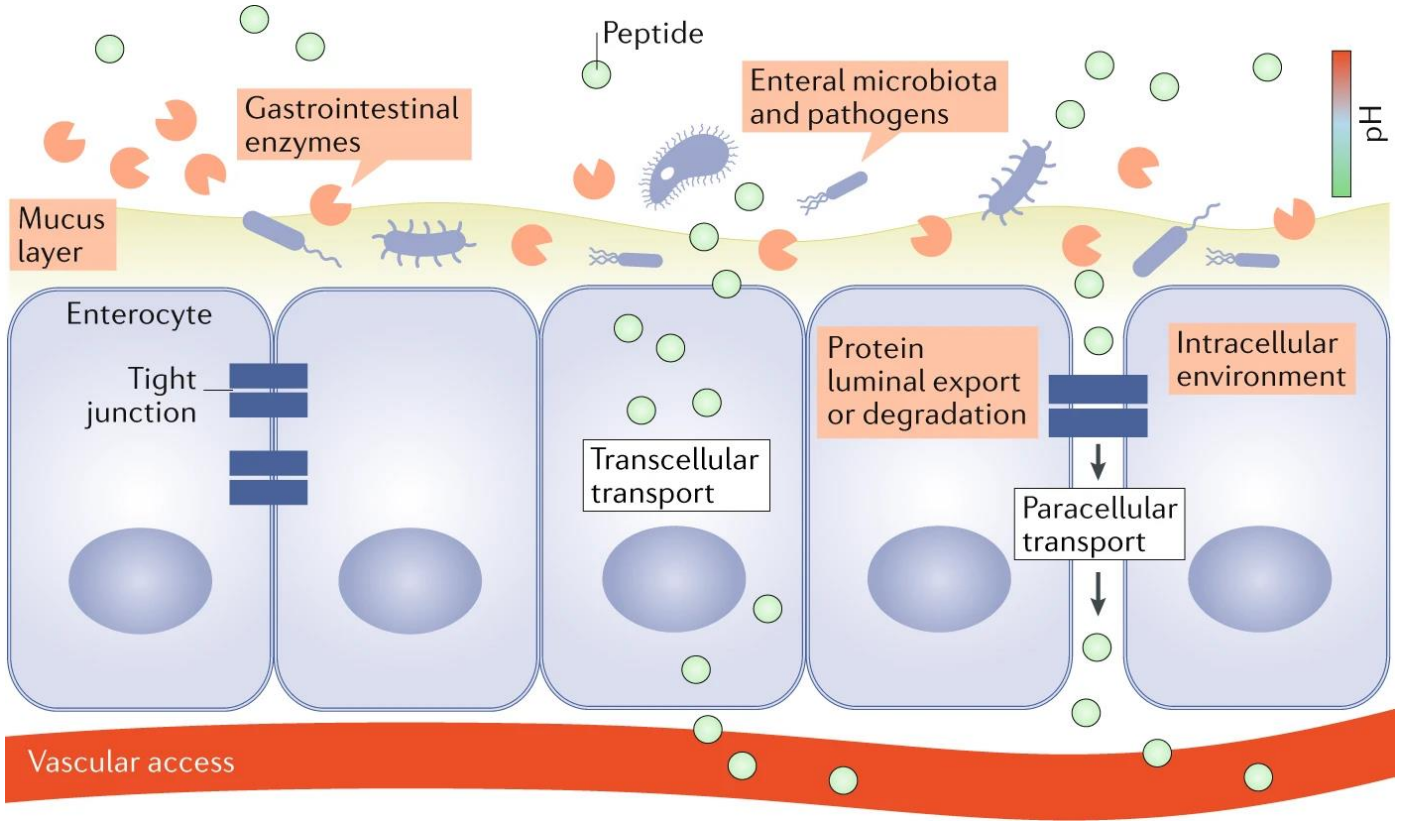


Improved patient compliance

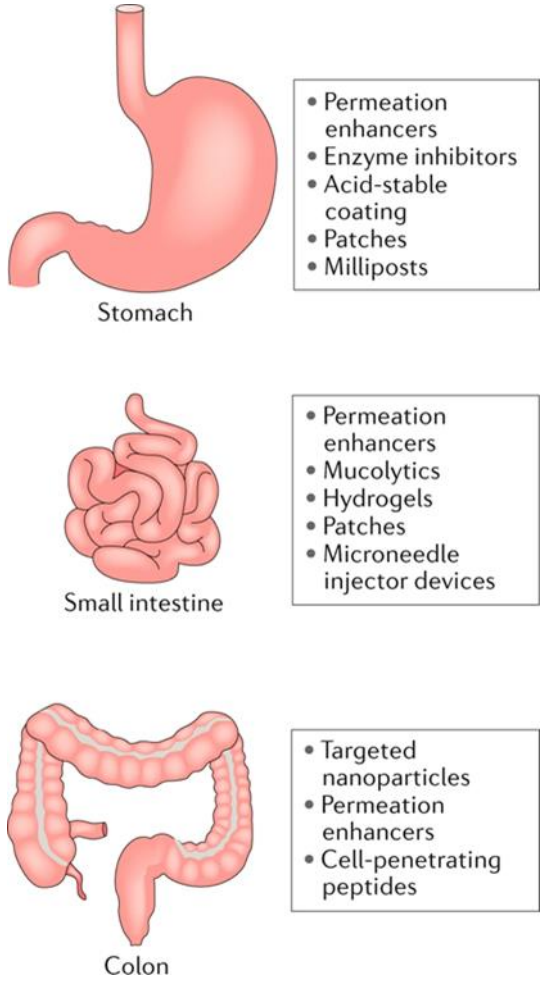


Oral peptide delivery – Challenges

Oral peptide delivery requires the circumvention of multiple structural and functional barriers:

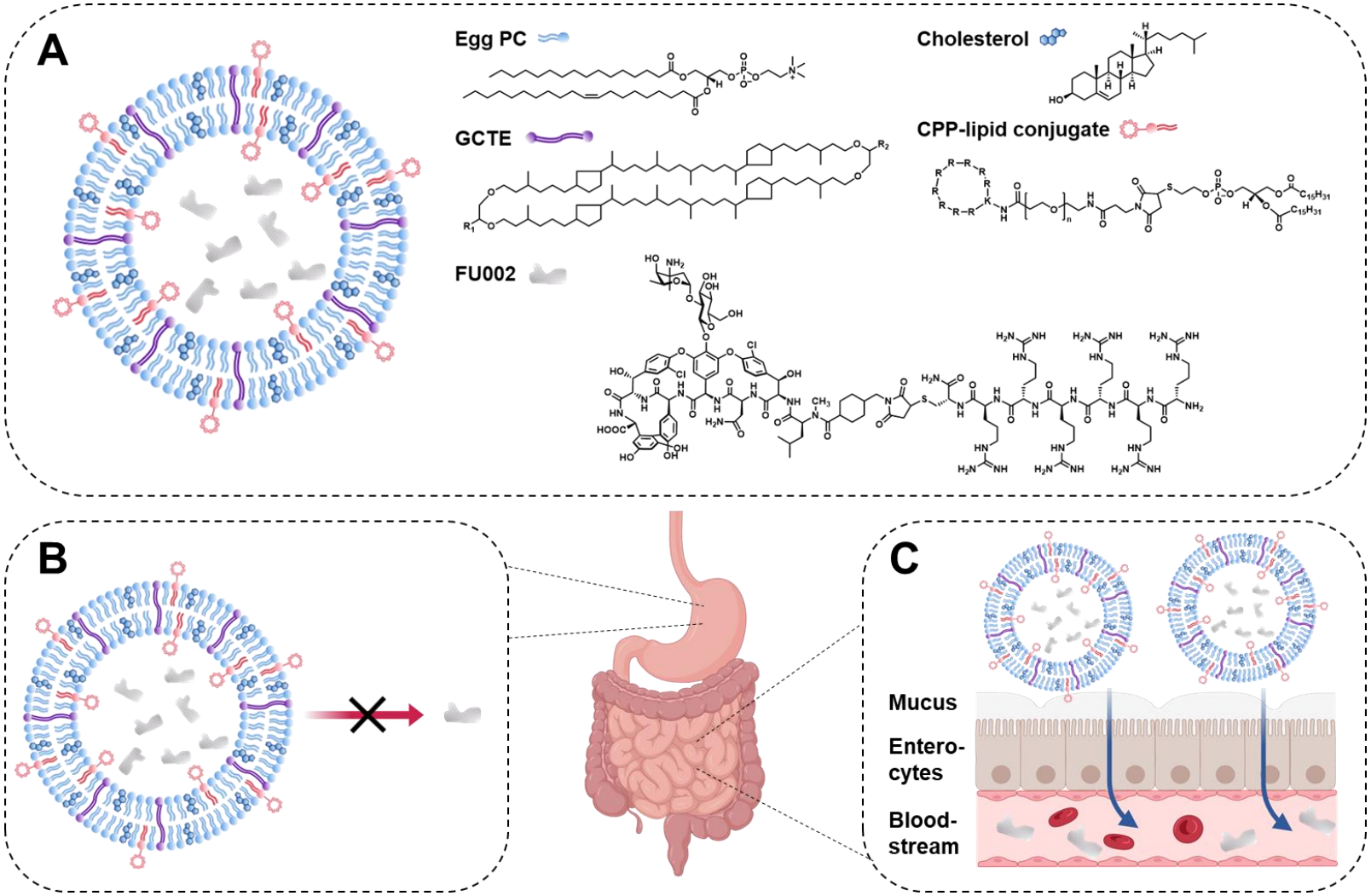


Strategies applied:



Adapted from: Drucker, Daniel J. Nature Reviews Drug Discovery 19 (2020): 277-289.

Strategy: TELs and CPP-phospholipid-conjugate



Key features:

- **Tetraether lipids (GCTE)**
  Non-GMP
- **CPP-conjugate:**
  GMP-compliant
  Non-toxic (rodents, dogs)
- **Peptide therapeutics**
  Bulevirtide
  Vancomycin
  FU002 (preclinical development)
  GLP-1 analogues (ongoing)

Werner, J. et al., Adv. Healthc. Mater. 2024, 13, 2303654.

Role of tetraether lipids in oral peptide delivery

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TEL-containing formulations:

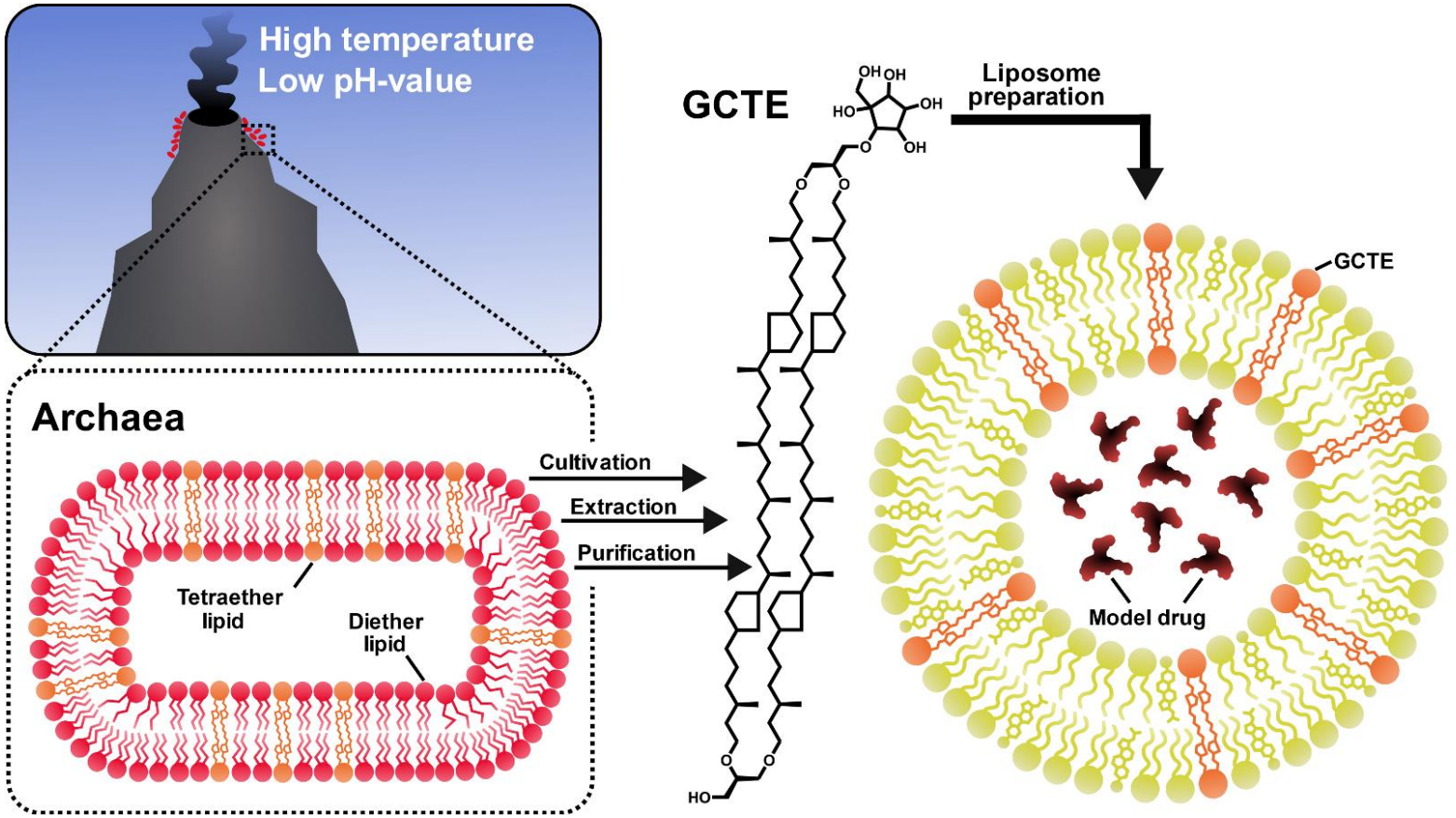
- phospholipid-based formulations
- minor amount of TELs

Added value of TELs:

- bilayer stabilization
- prevention of leakage
- permeation enhancing effect?

Limitations:

- complex process
- synthesis not yet possible
- availability / regulatory issues



Mühlberg, E. et al., Nanomedicine 2021, 16, 1813-1832.
Uhl, P. et al., Eur. J. Pharm. Sci. 2017, 108, 111-118.
Uhl, P. et al., Eur. J. Pharm. Biopharm. 2016, 103, 159-166.

Tetraether lipid liposomes for oral peptide delivery

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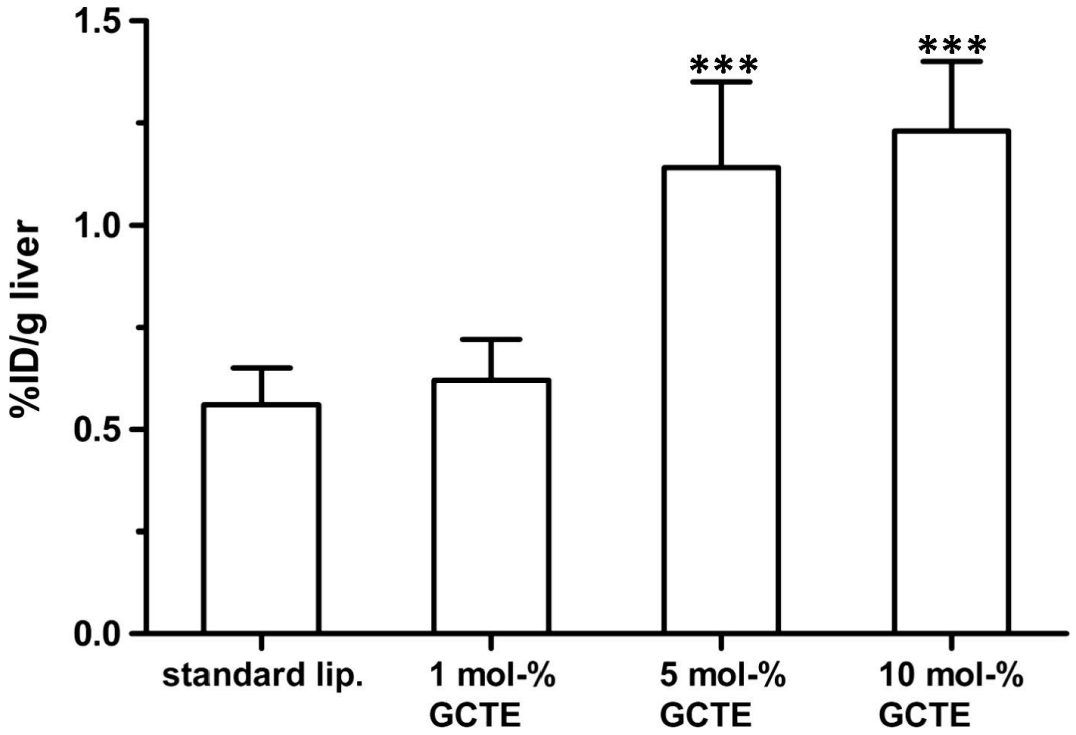
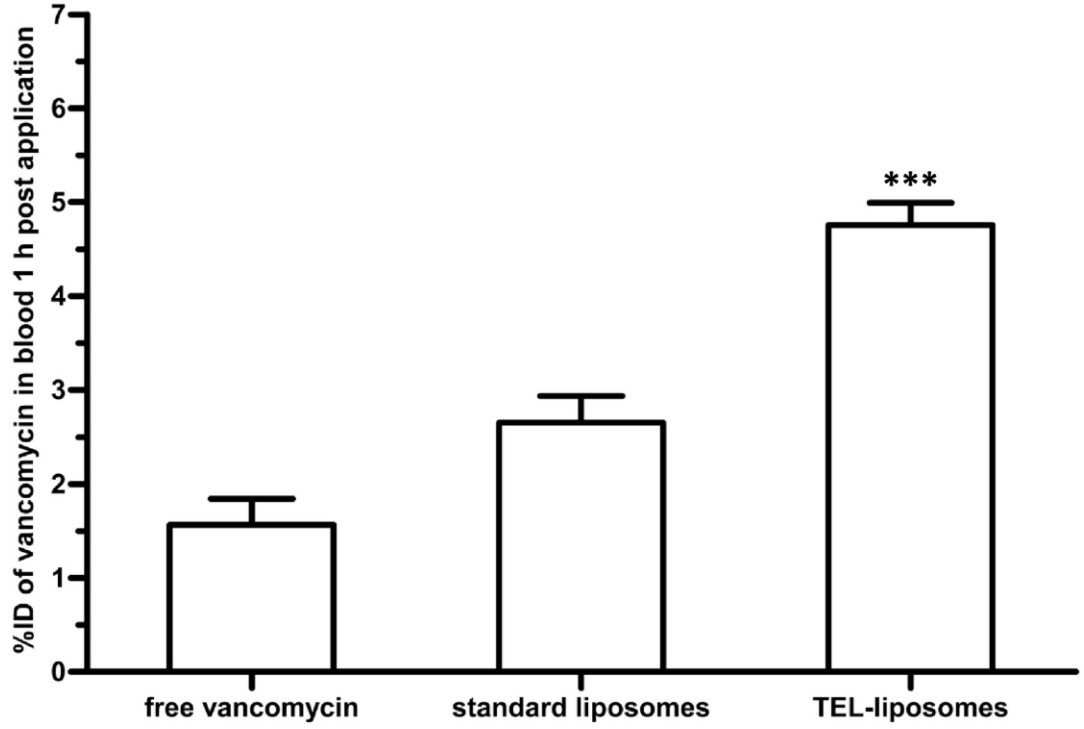
Oral delivery of bulevirtide (Hepcludex®)



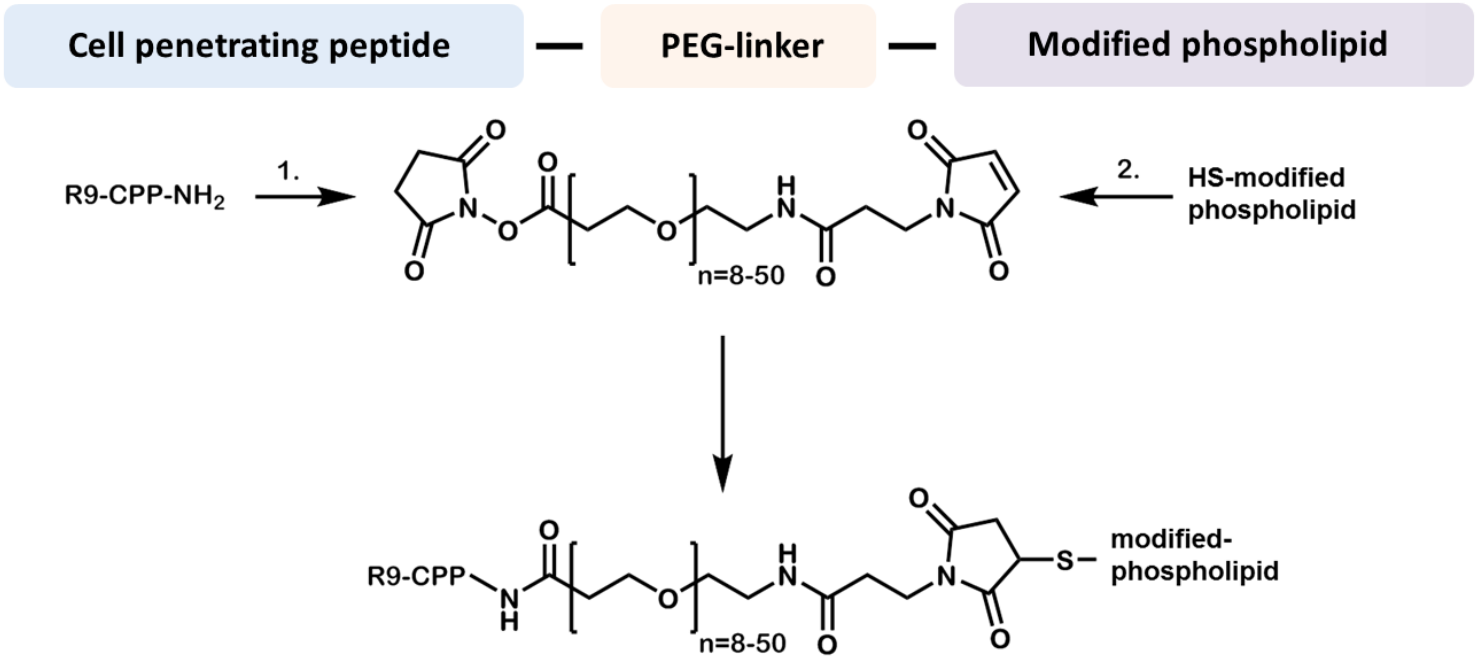
Uhl, P. et al., Eur. J. Pharm. Biopharm. 2016, 103, 159-166.

Oral delivery of vancomycin

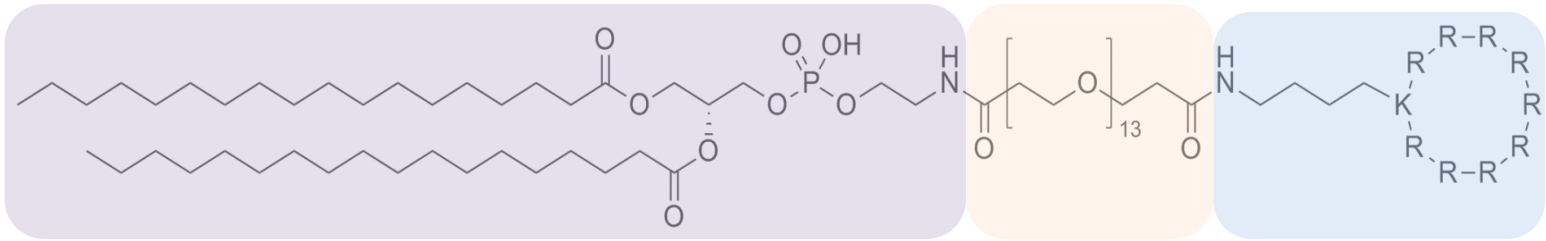


Uhl, P. et al., Eur. J. Pharm. Sci. 2017, 108, 111-118.

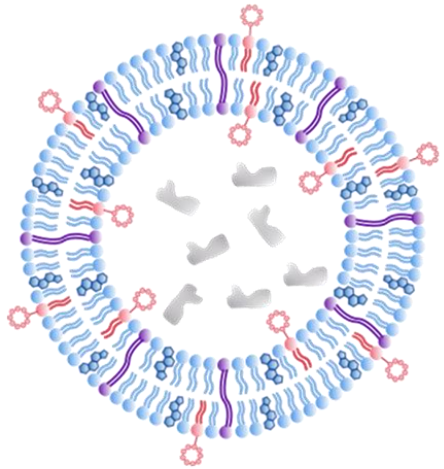
CPP-phospholipid-conjugate

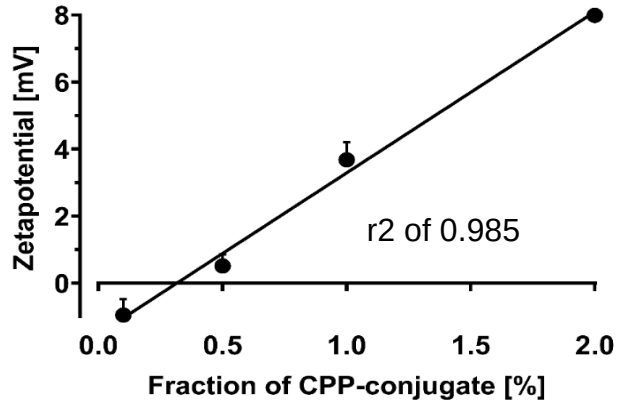


Patent: WO2017067642A1.



Lipophilic anchor *PEG-linker* *CPP*

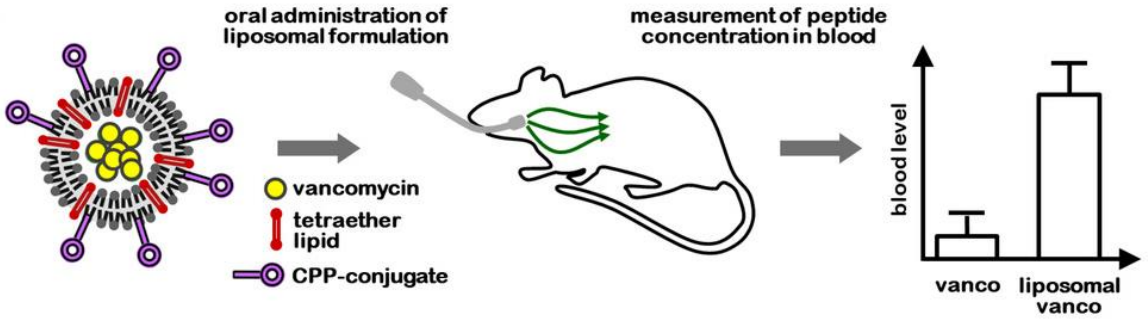




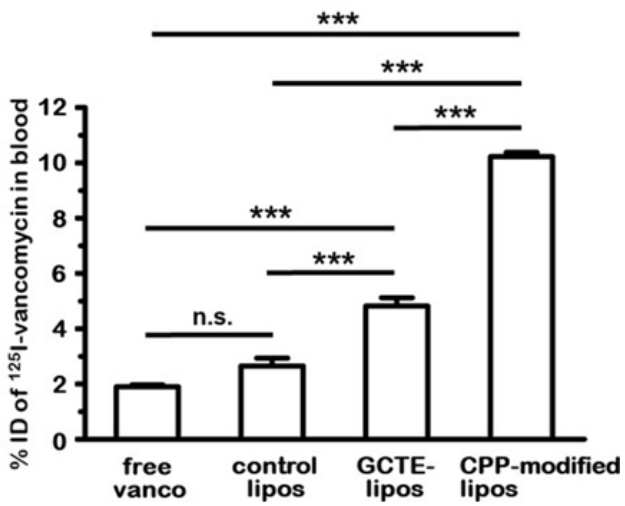
Uhl, P. et al., Adv. Therap. 2023, 6, 2300021.

Animal studies of liposomal vancomycin

Are results from rodent studies transferable to higher mammals?

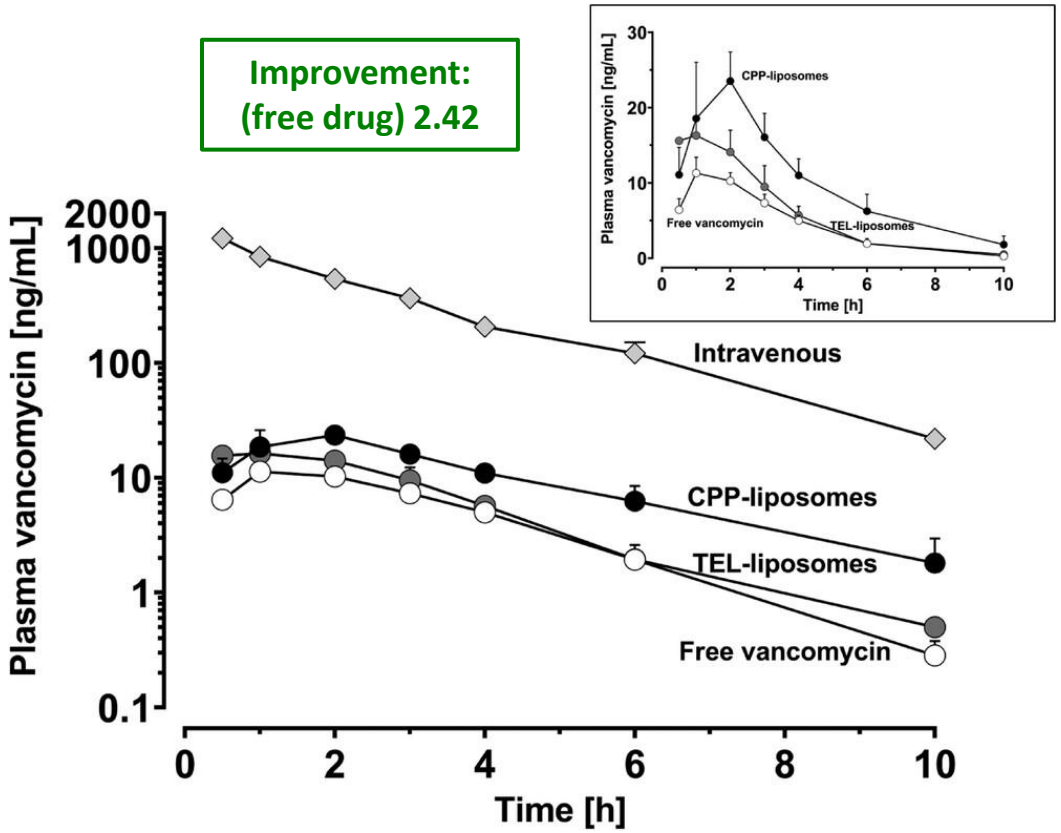


Improvement: (free drug) 5.16



Uhl, P. et al., Adv. Therap. 2021, 4, 2000247.

Improvement: (free drug) 2.42



Uhl, P. et al., Adv. Therap. 2023, 6, 2300021.

ROVANCE – to overcome bacterial resistance

ROVANCE improved antibiotics

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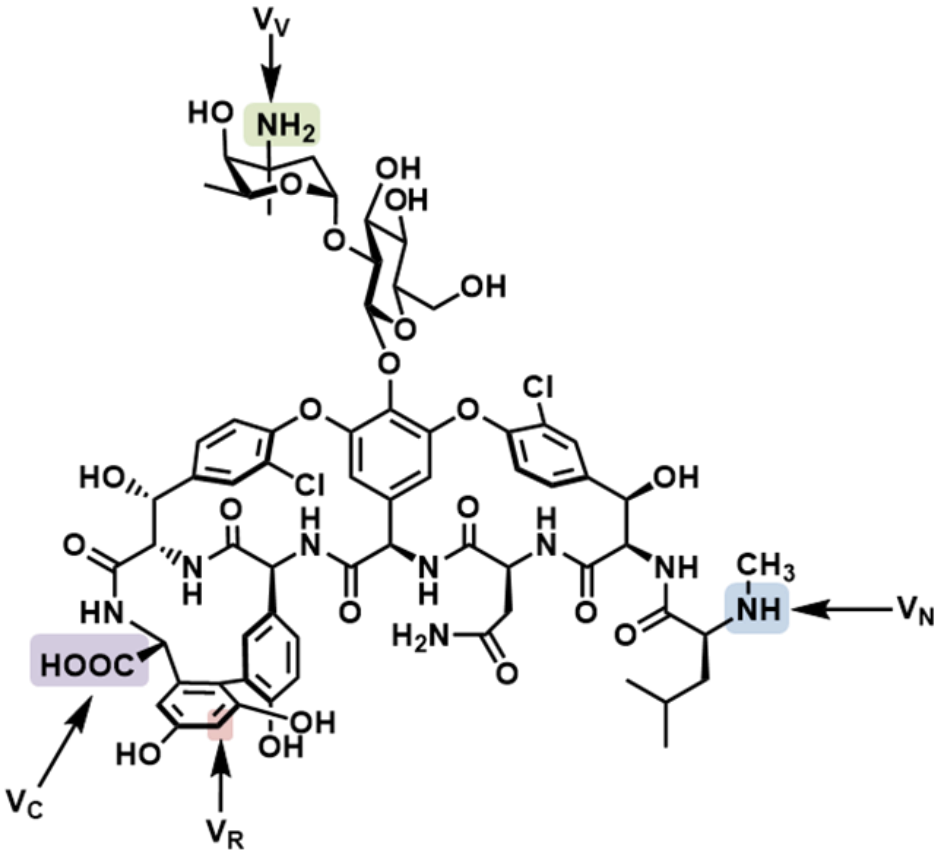
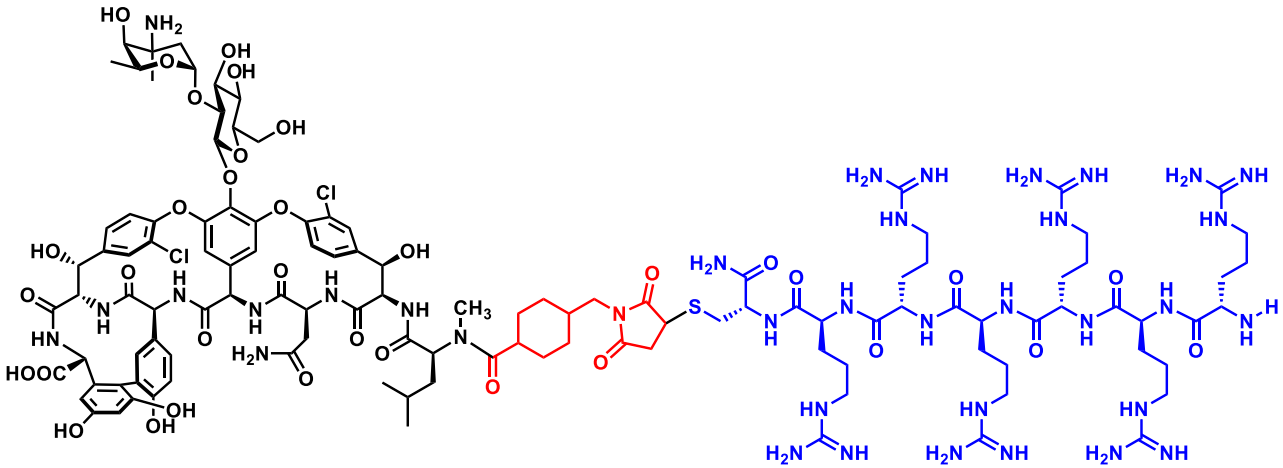
ROVANCE library: > 100 derivatives



Patent application WO 2020/094015

Lead candidate FU002 (preclinical development)

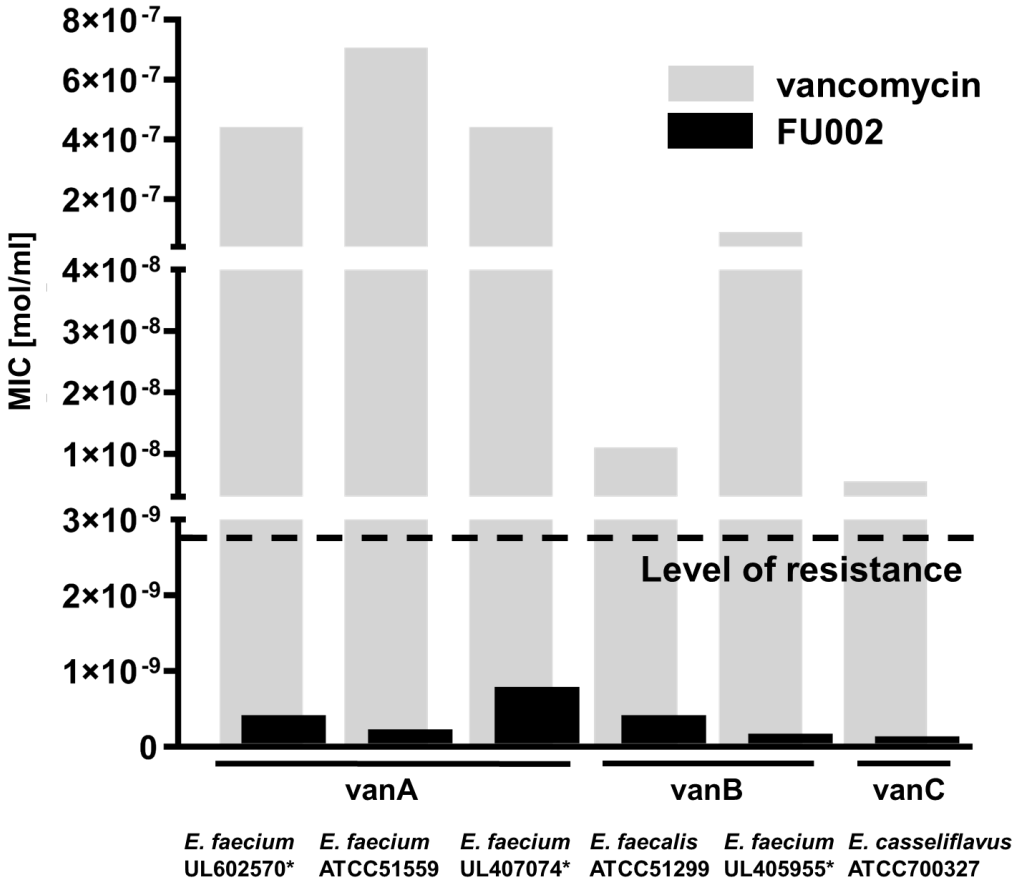


vancomycin **linker** **polycationic peptide**

Umstätter, F. et al., Angew. Chem. Int. Ed. 2020, 59, 8823-8827.

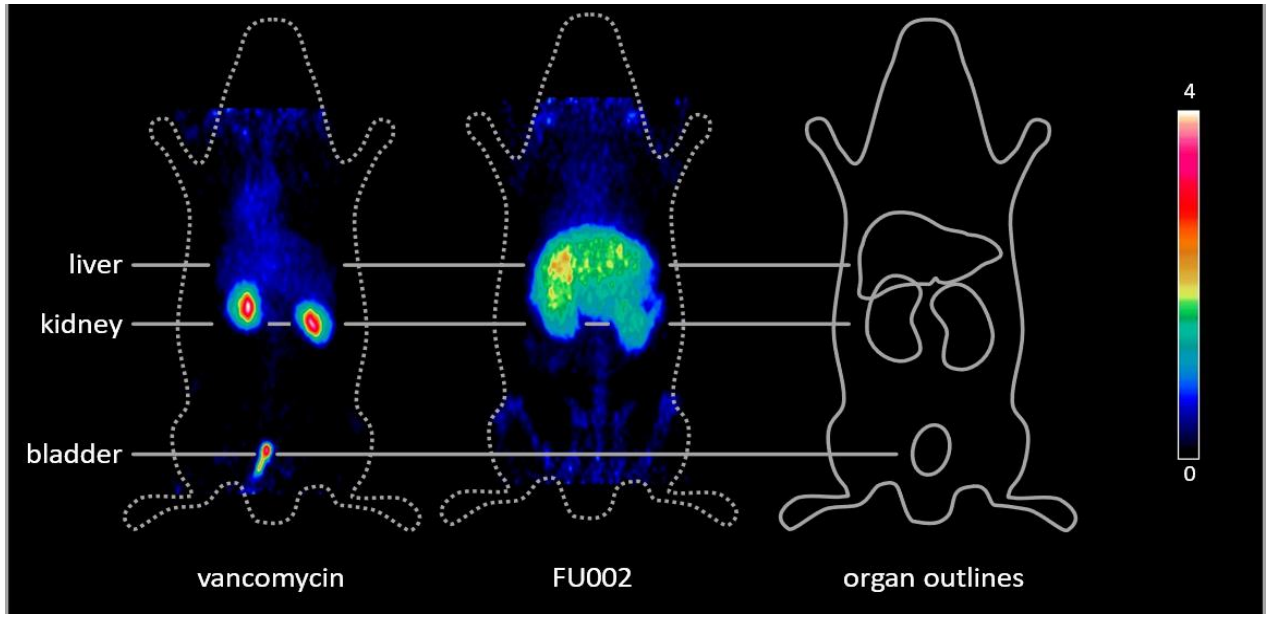
ROVANCE – to overcome bacterial resistance

FU002: high activity on resistant enterococci



Umstätter, F. et al., Angew. Chem. Int. Ed. 2020, 59, 8823-8827.
Mühlberg, E. et al., Pharmaceuticals 2020, 13:110.

Biodistribution profile

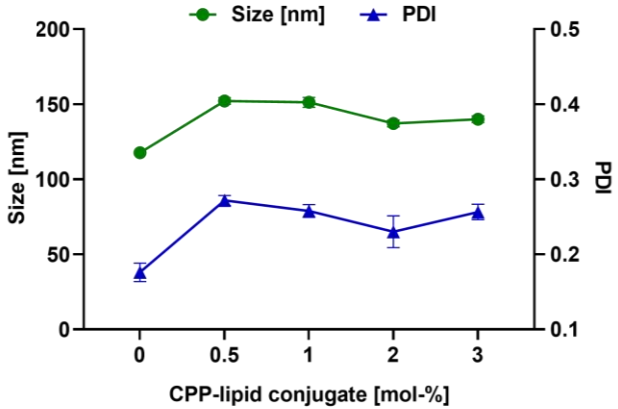


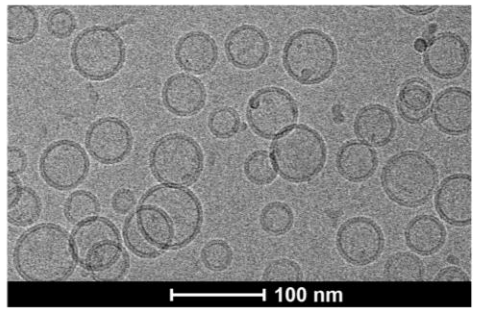
FU002

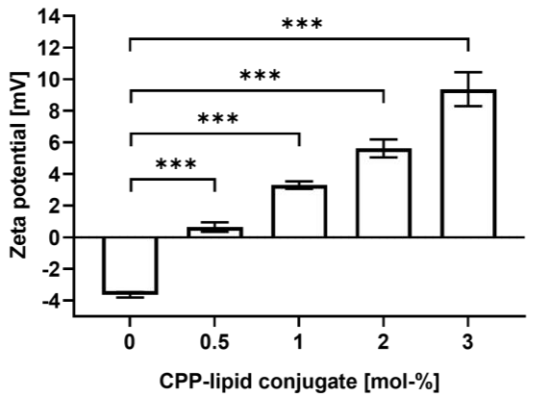
- resistance breaking (*in vitro* and *in vivo*)
- altered biodistribution profile
- limitation: low oral bioavailability

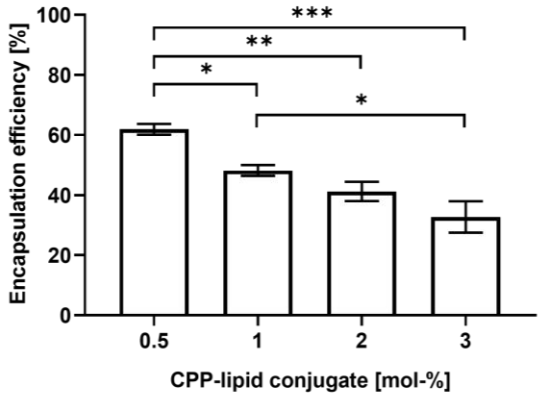
In vitro studies with liposomal FU002

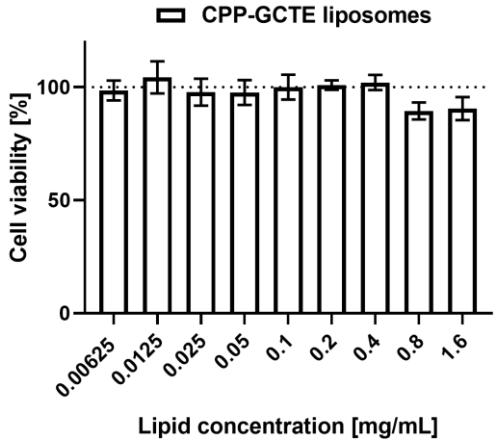
Characterization of liposomes

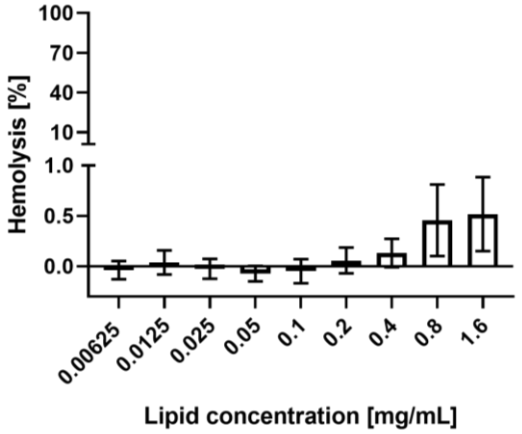


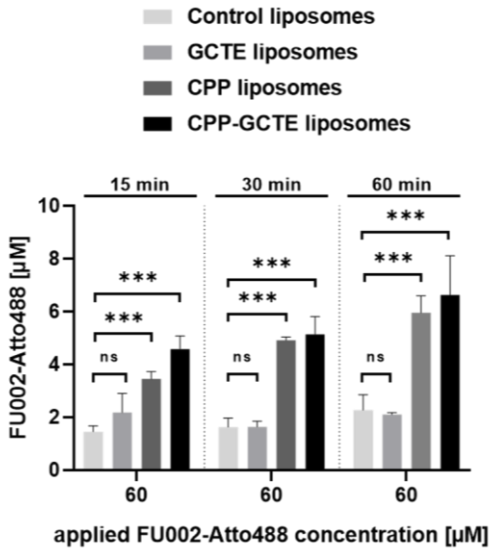








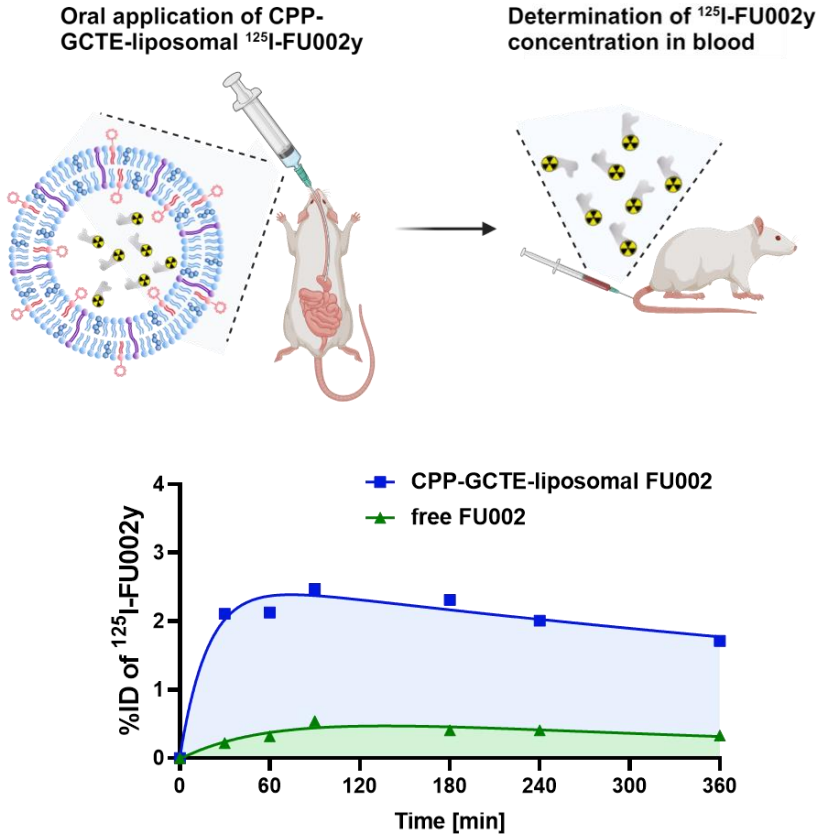




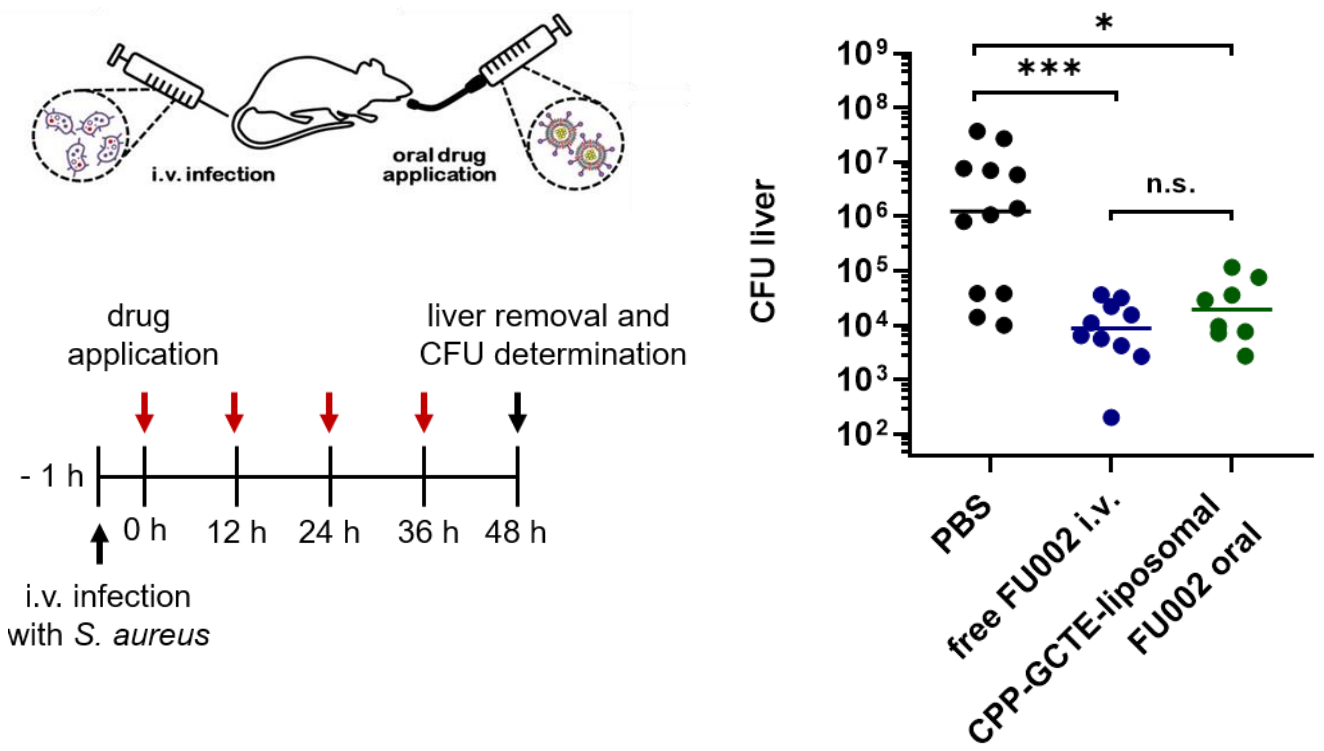
Werner, J. et al., Adv. Healthc. Mater. 2024, 13, 2303654.

Liposomal formulation of FU002 – *in vivo* studies

In vivo pharmacokinetics in rats



In vivo efficacy in a murine systemic infection model



Werner, J. et al., Adv. Healthc. Mater. 2024, 13, 2303654.

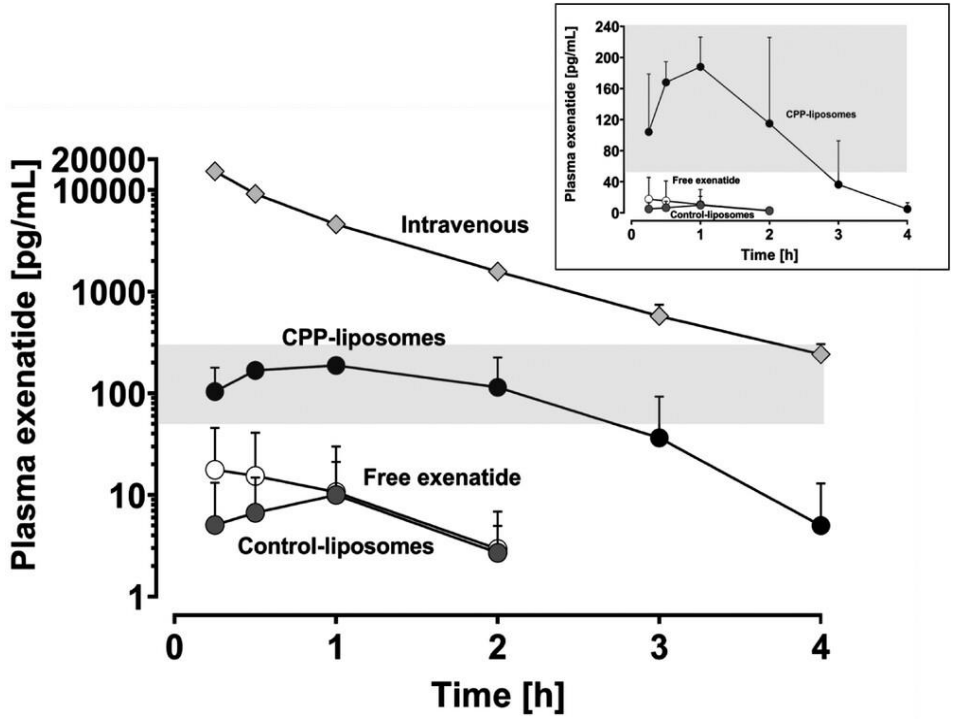
Liposomes as platform technology?

Results obtained with CPP-liposomes

Model drug	Rodents	Beagle dogs
Vancomycin	5.16*	2.42*,$
Exenatide	14.21*,§	18.80*,#
FU002	5.38*	---

* Effect only in fasted state
$ Oral bioavailability: 3.90%
§ Oral bioavailability (**GCTE-liposomes**): **0.426%**
# Oral bioavailability: **0.29%**

CPP-liposomes: oral exenatide

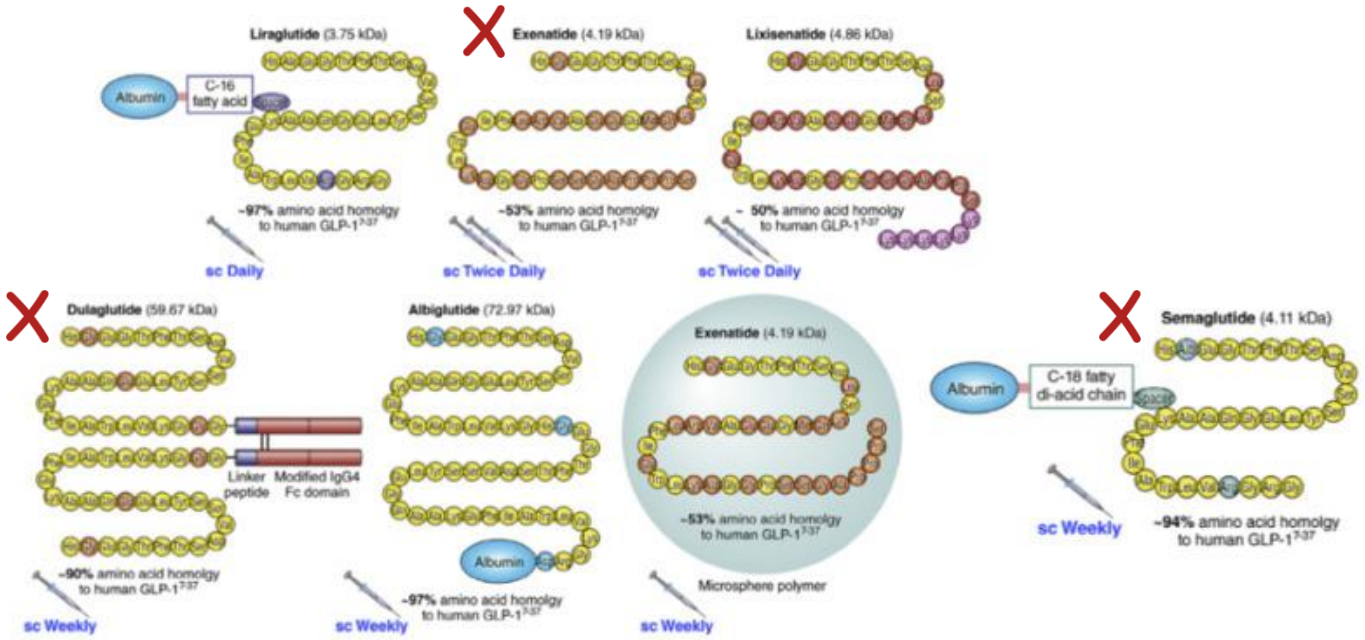


Uhl, P. et al., Adv. Therap. 2023, 6, 2300021.

GLP-1 analogues: Ideal for platform testings

Liposomes as platform technology?

GLP-1 analogues: Overview



https://www.ncbi.nlm.nih.gov/books/NBK279141/figure/pharmaco-agent-diab2.F10/

Liposomal characteristics

Herbster, L. unpublished data.

Liposomes as platform technology?

Liposomal uptake

Uptake of GLP-1 analogues

Herbster, L. unpublished data.

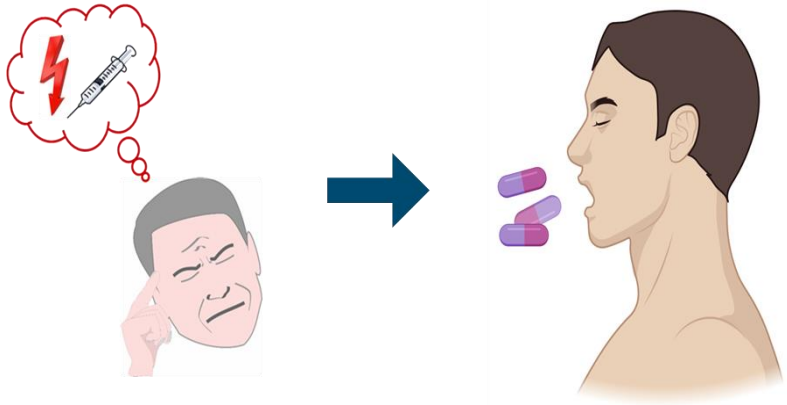
Summary

Results obtained

- Increased oral bioavailability of vancomycin (rodents and dogs)
- Increased oral bioavailability of FU002 (rodents, therapeutic efficacy)
- Increased oral bioavailability of exenatide (rats and dogs)
- GLP-1 analogues study ongoing

Platform technology for oral peptide delivery?

- Availability of TELs and CPP-conjugate
- Application range of technology
- Transferability of animal data to humans



Thank you for your attention!

Thanks to:

<u>My team at Heidelberg University</u>

- Julia Werner, Lorenz Herbster (Liposomes)
- Florian Umstätter, Eric Mühlberg (FU002)

<u>The cooperation partners</u>

- Ohlsen lab (Würzburg)
- Fricker/Mier lab (Heidelberg)
- And many more….

<u>The funding agencies</u>

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