Tech Session II: Oral Delivery I

Deborah E. Shalev

CRS 2025 ANNUAL MEETING & EXPOSITION
PHILADELPHIA, PA
JULY 13-18, 2025

NEXT-GENERATION DELIVERY INNOVATIONS

Azrieli College of Engineering Jerusalem

עזריאלי מכללה אקדמית להנדסה ירושלים

Developing an Oral Formulation for the Anti-Prostate Cancer Drug Leuprorelin

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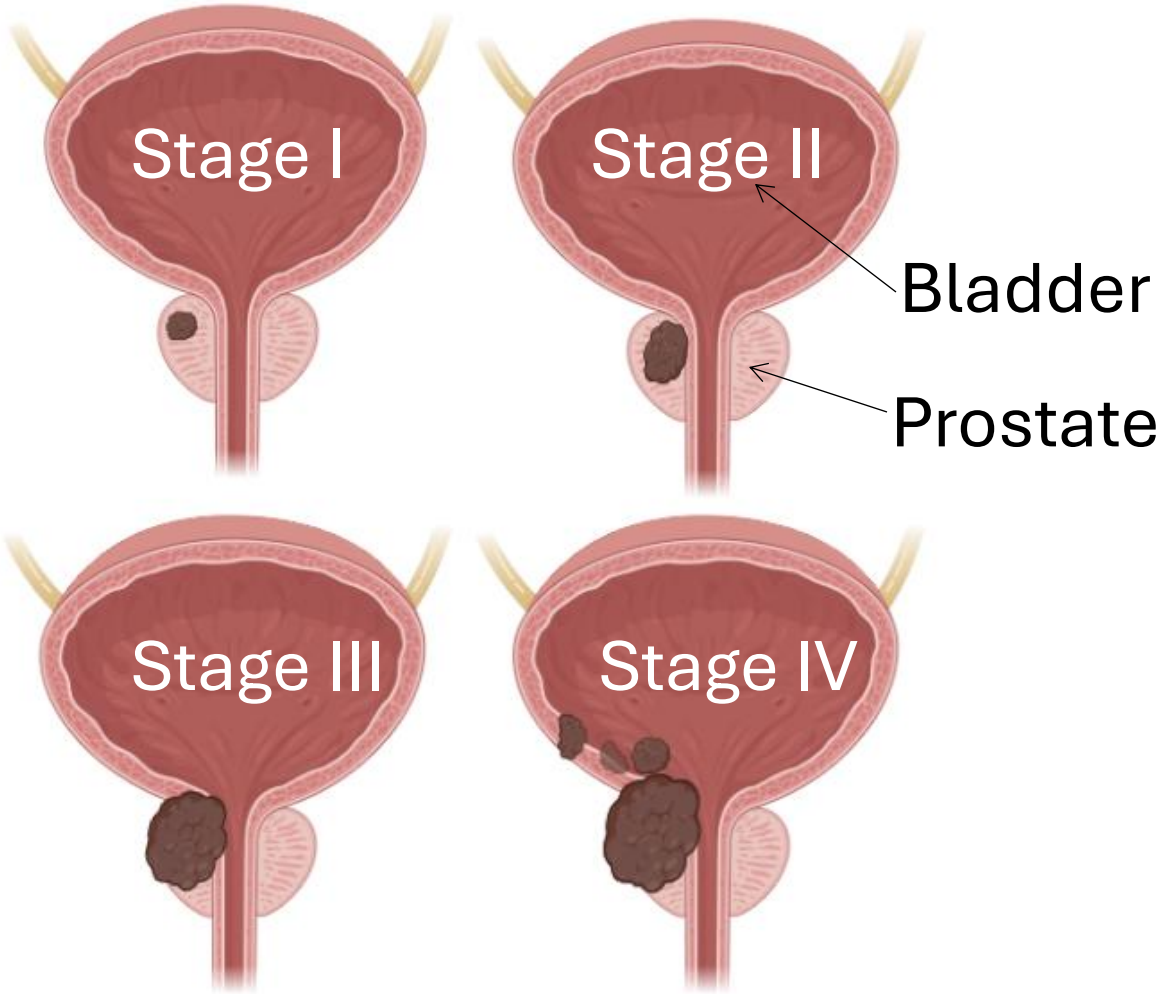
NEXT-GENERATION DELIVERY INNOVATIONS

Over 1 in 8 men will be diagnosed with prostate cancer during their lifetime*

80% of all cases will survive 10 years or more†

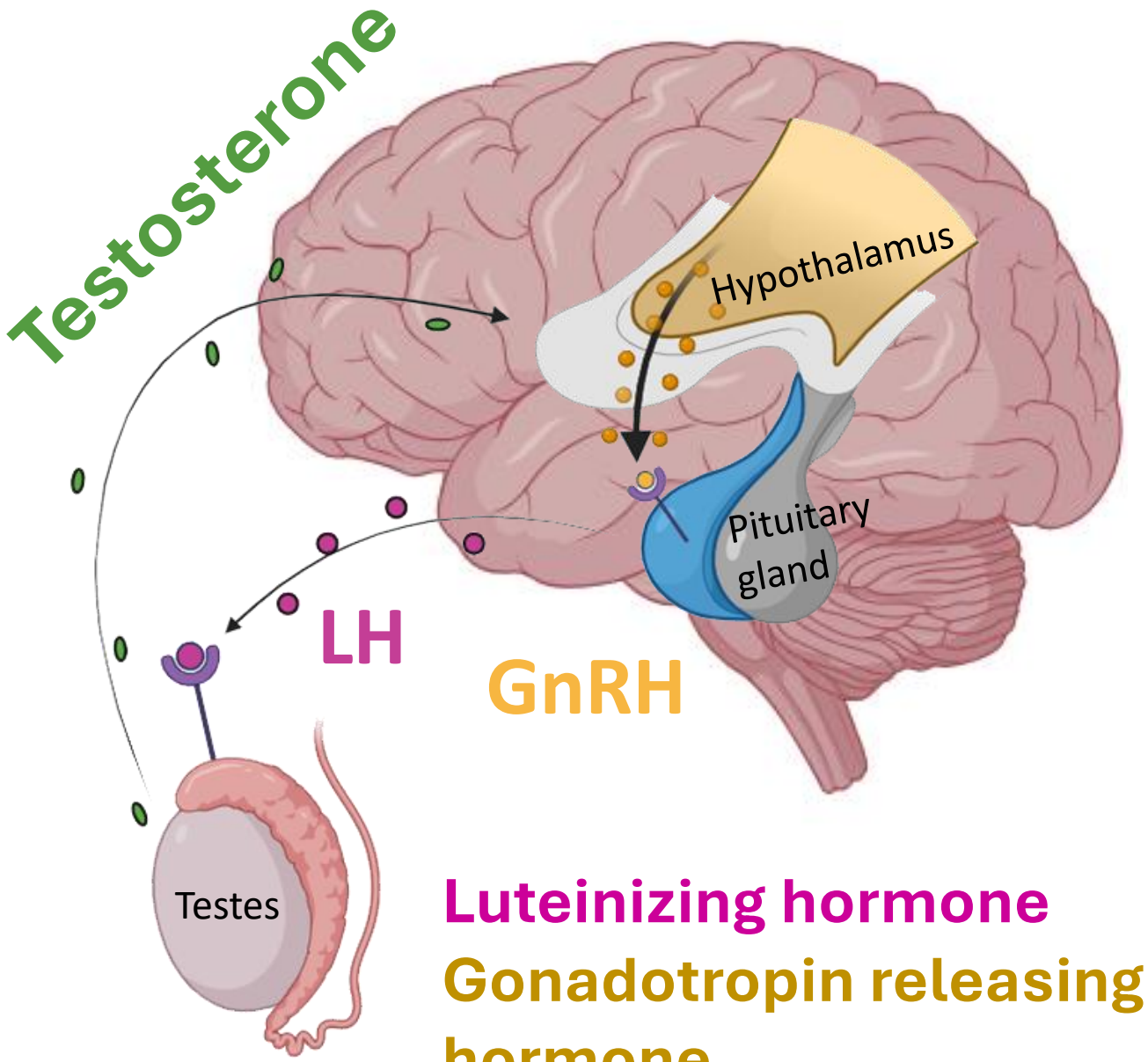


* *National Cancer Institute*

† *Cancer Research UK*

Leuprorelin is a GnRH agonist that desensitizes the GnRH receptor.

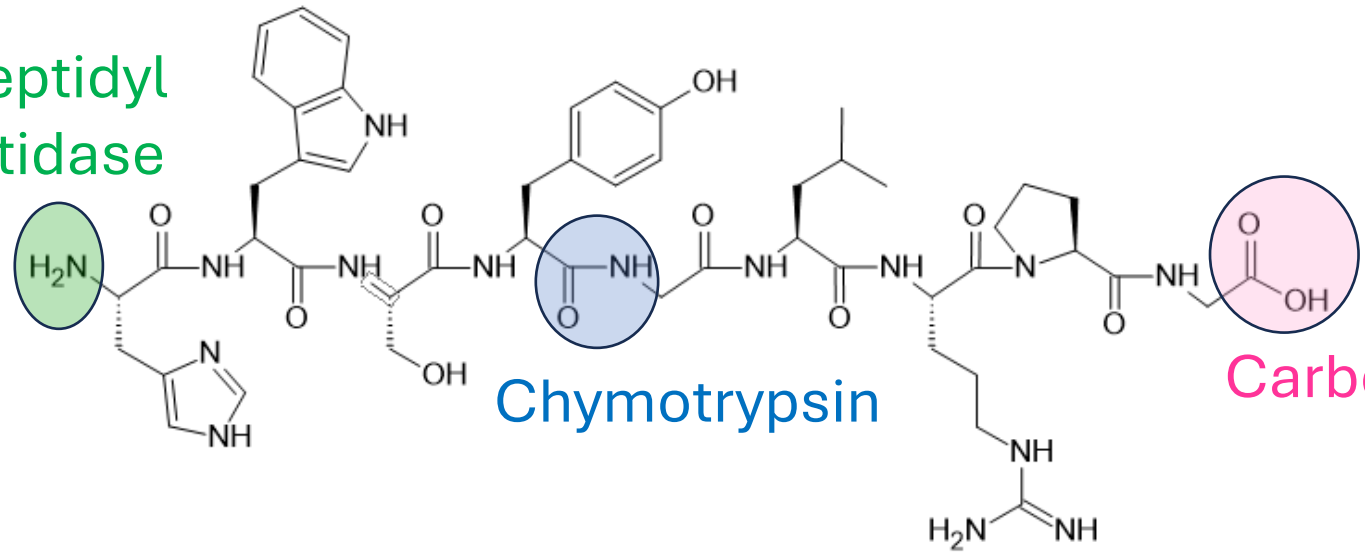
Leuprorelin is currently administered intramuscularly.



Luteinizing hormone
Gonadotropin releasing hormone

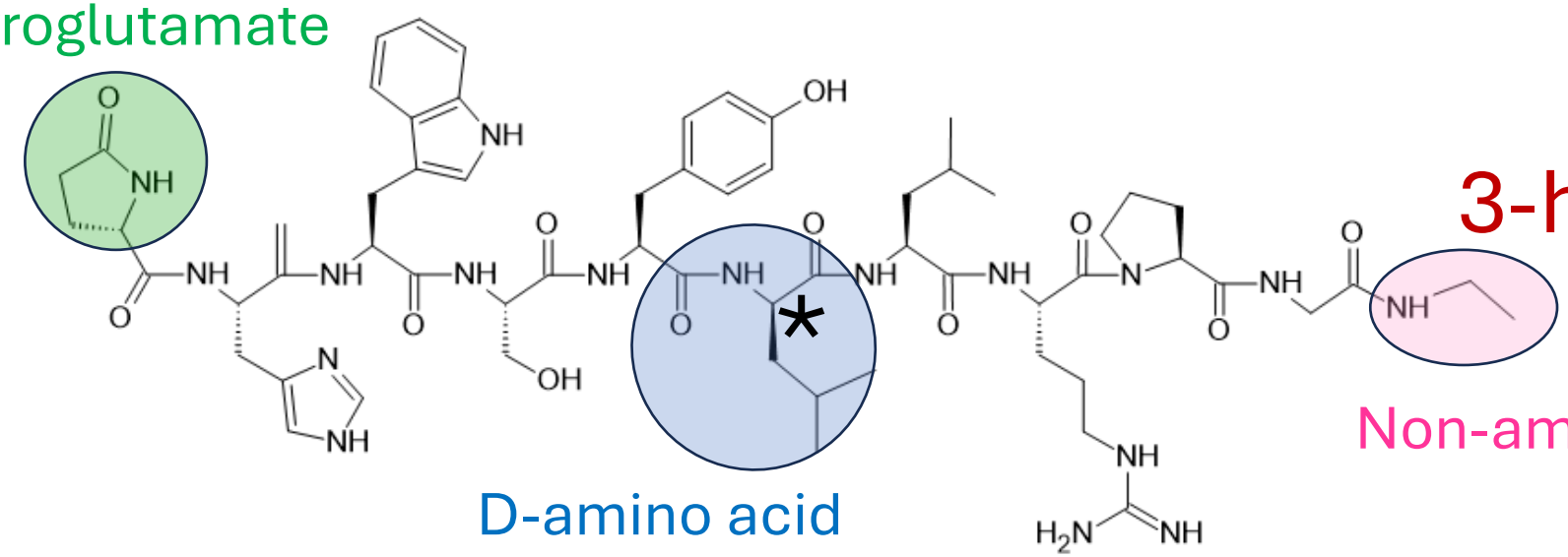
Leuprorelin is much more stable than GnRH

GnRH



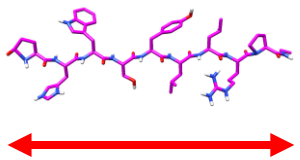
Circulating half-life
3-4 min

LP

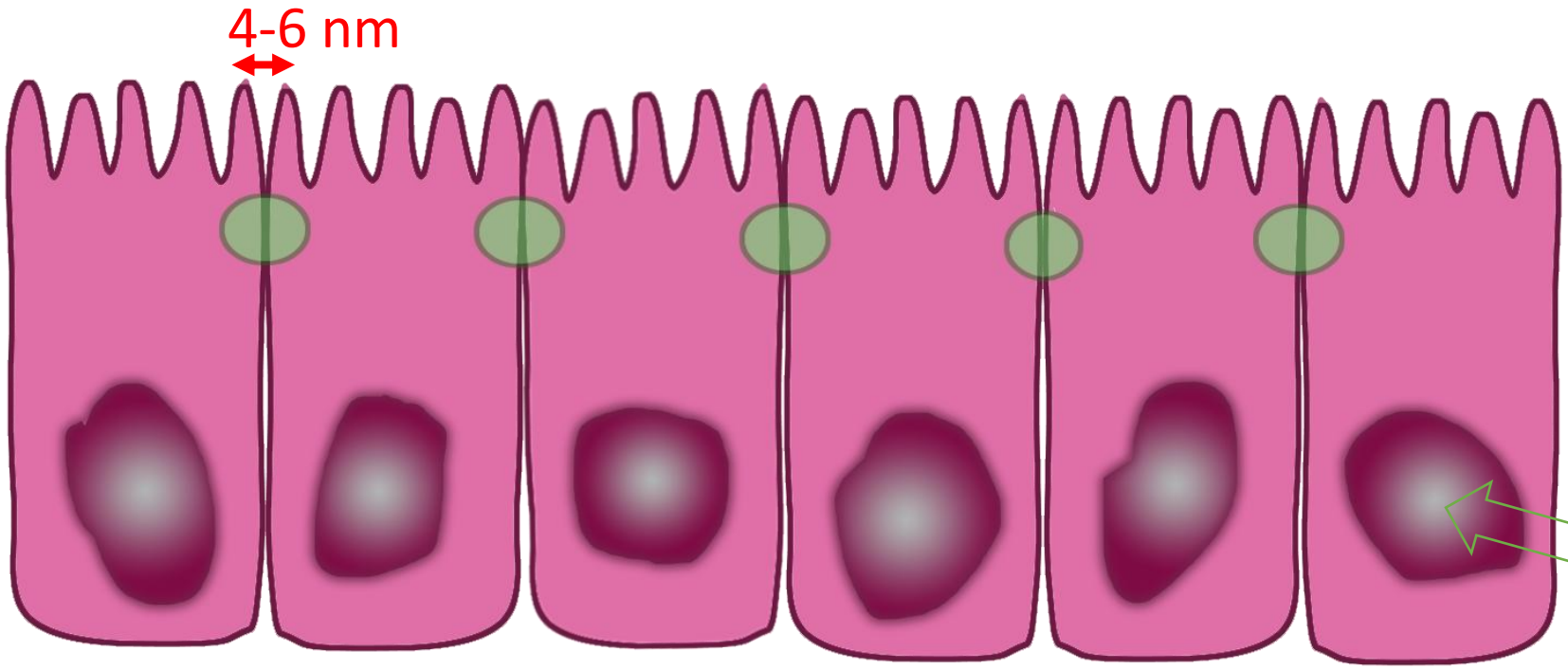


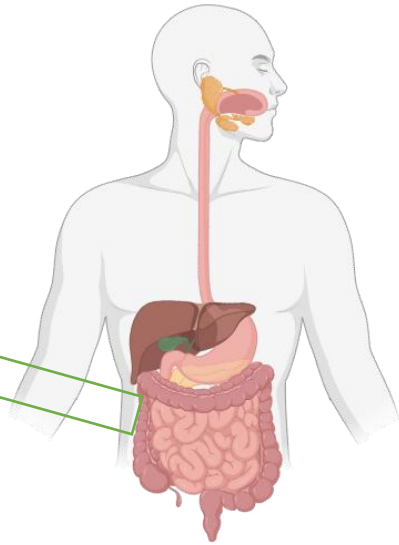
3-hour

Extended leuprorelin is too large to traverse the tight-junctions



3.5 nm

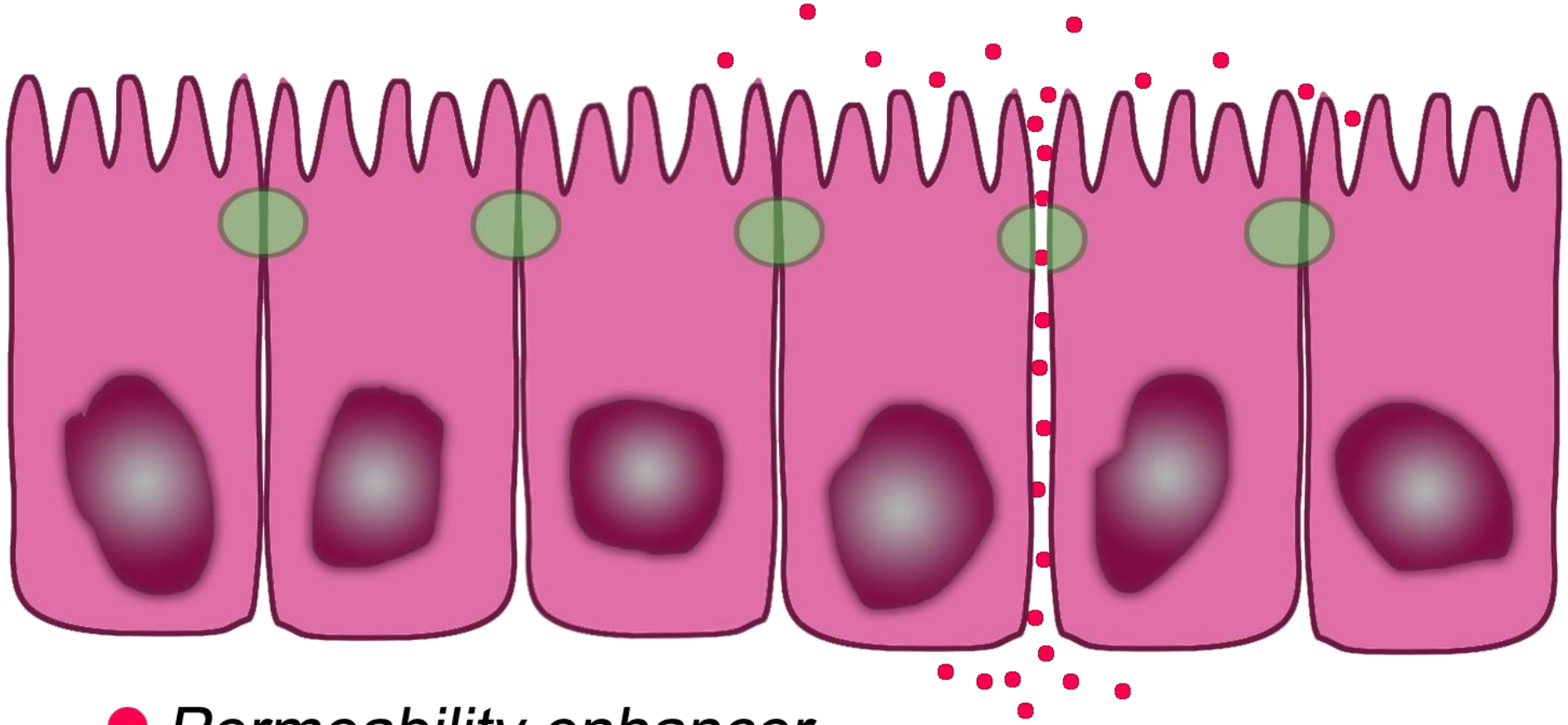




Tight junctions

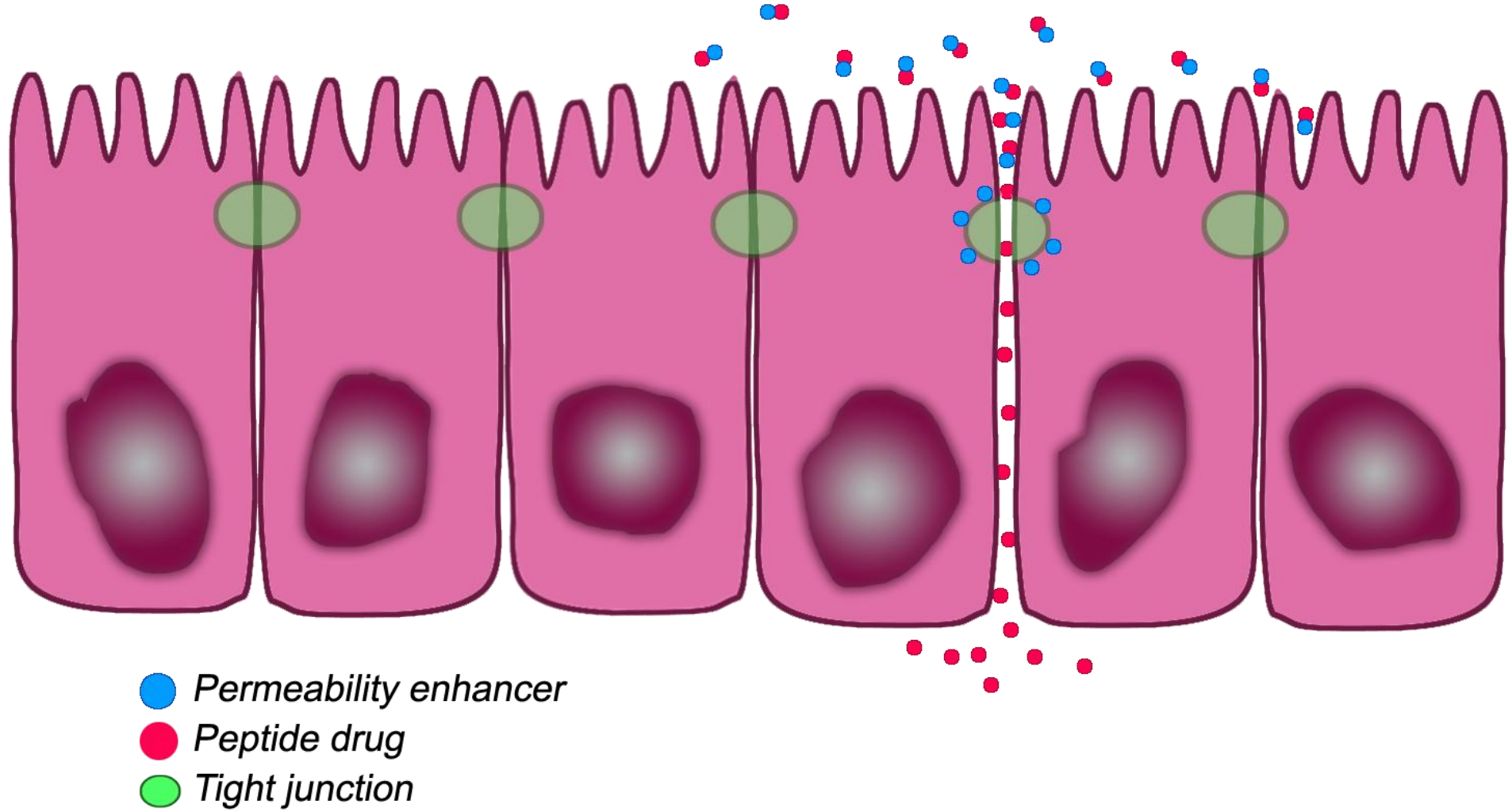
Credit: BioRender.com

Permeability enhancers are required to locally disrupt the membranes

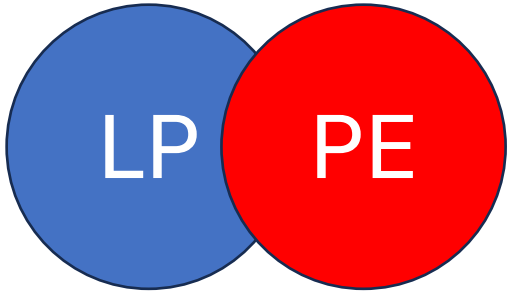


Our strategy:

Leuprorelin-permeability enhancer complex will travel together to the tight-junction.



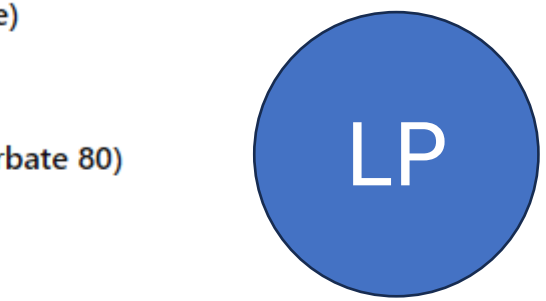
We screened several permeability enhancers by NMR for interactions with leuprorelin

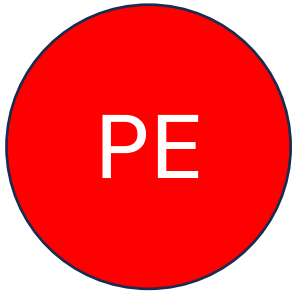


Sure! Here's a list of permeability enhancers:

1. Sodium Lauryl Sulfate (SLS)
2. Cationic Polymers (e.g., Polyethyleneimine)
3. Chitosan
4. Polysorbates (e.g., Polysorbate 20, Polysorbate 80)
5. Cyclodextrins
6. Fatty Acids (e.g., Oleic Acid)
7. Surfactants (e.g., Tween, Span)
8. Ethanol
9. Propylene Glycol
10. Azone (Lauric Acids)
11. Dodecylmethylsulfoxide (DMSO)
12. N-Methylpyrrolidone (NMP)
13. Bile Salts
14. Terpenes (e.g., Limonene)
15. Sodium Caprate

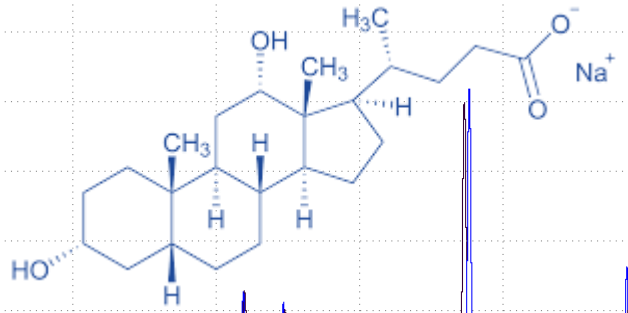
Let me know if you need more information on any of these enhancers!

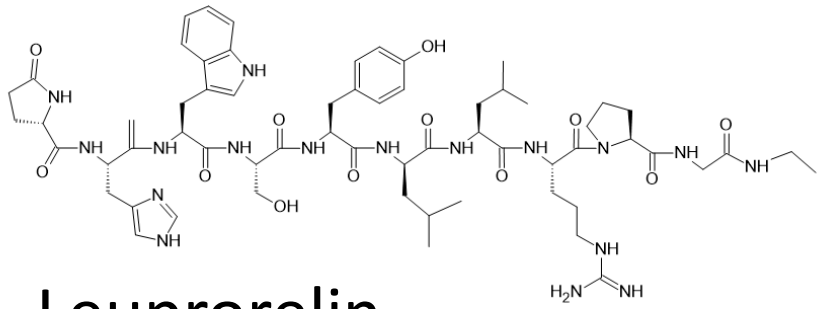




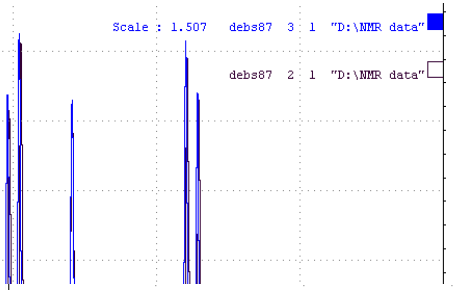
NMR showed no interaction with some permeability enhancers

Sodium deoxycholate





Leuprorelin



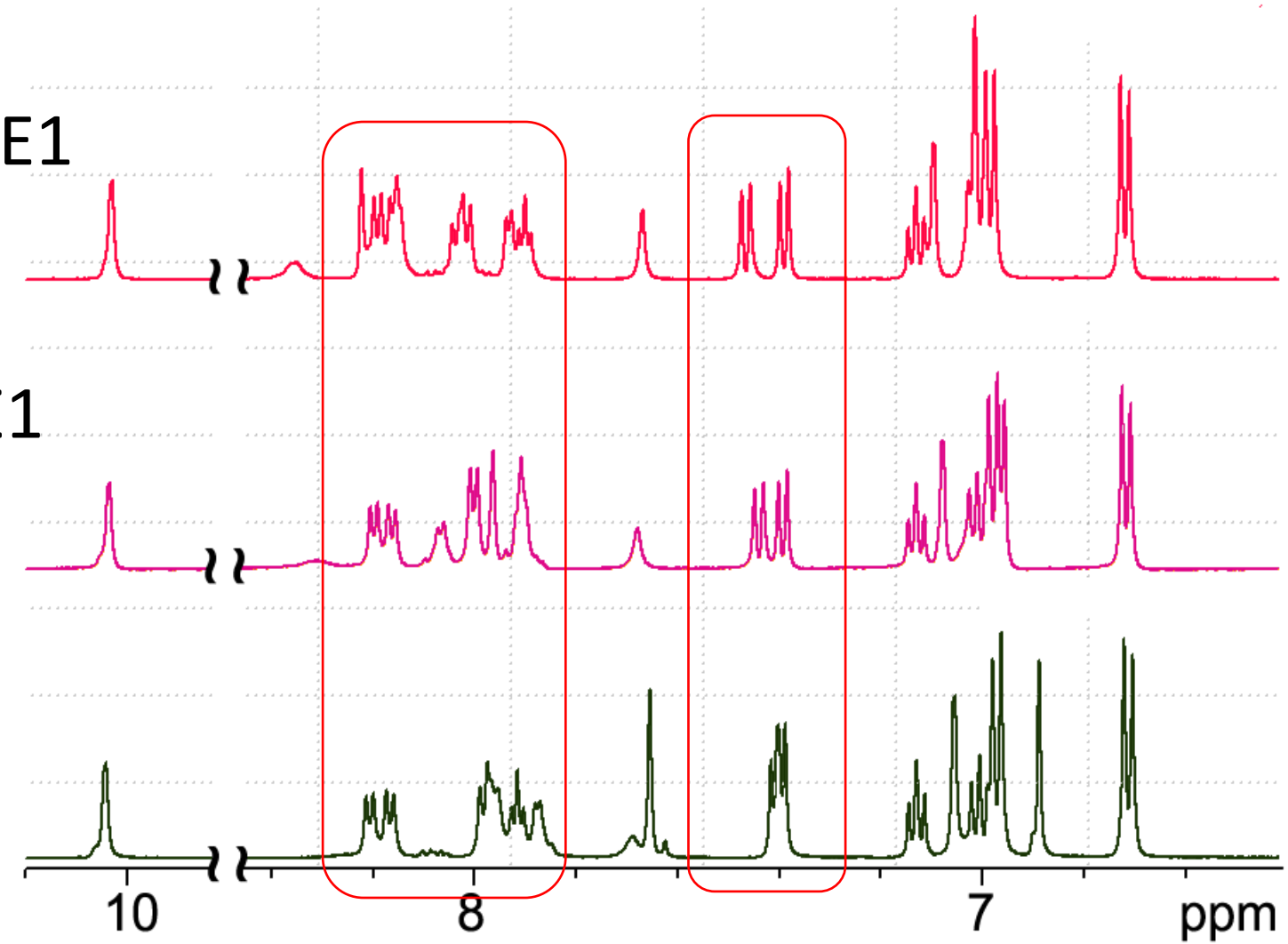
Sodium lauryl sulfate

Chemical shift deviations were dose-dependent

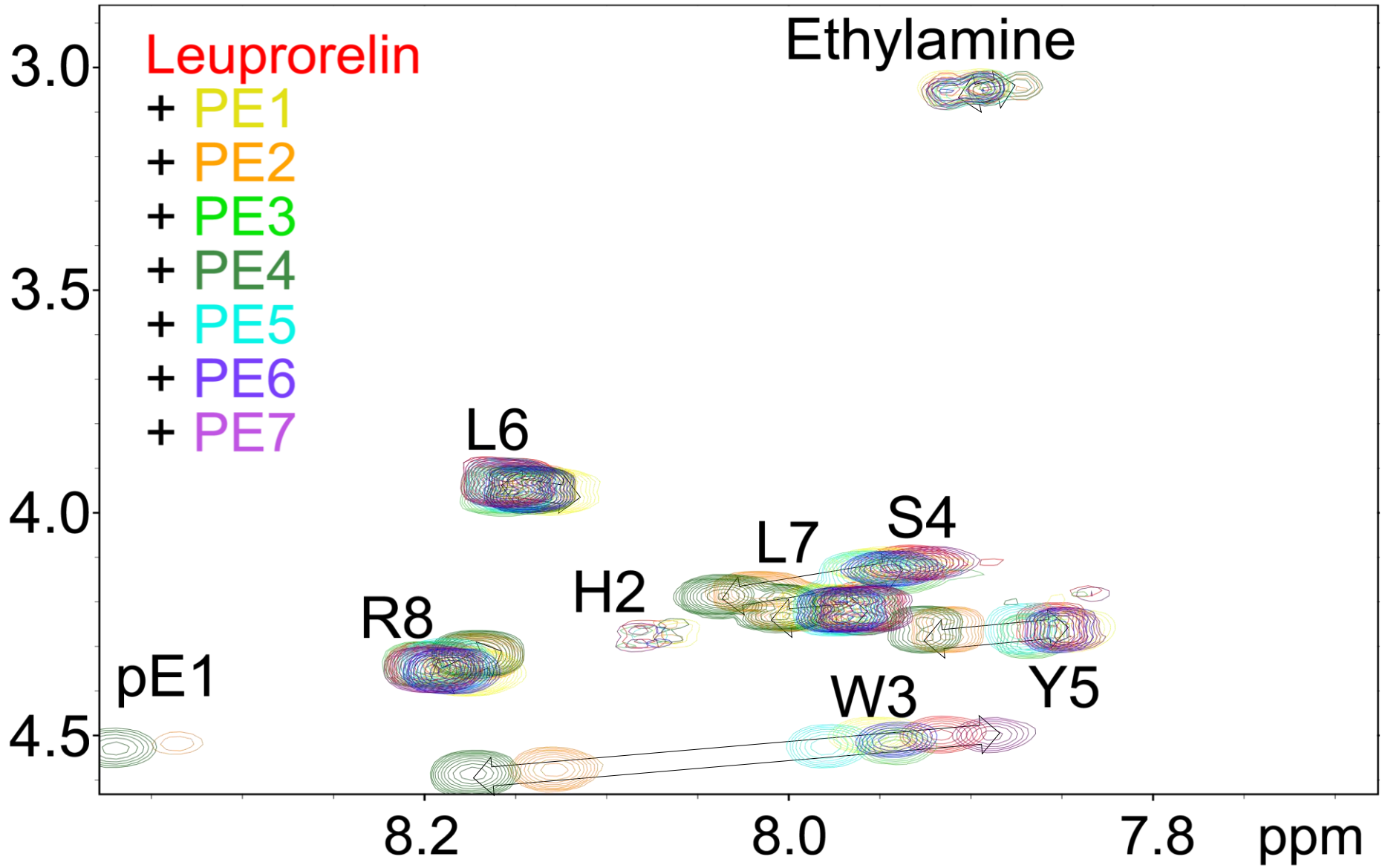
2 aliquots of PE1

1 aliquot of PE1

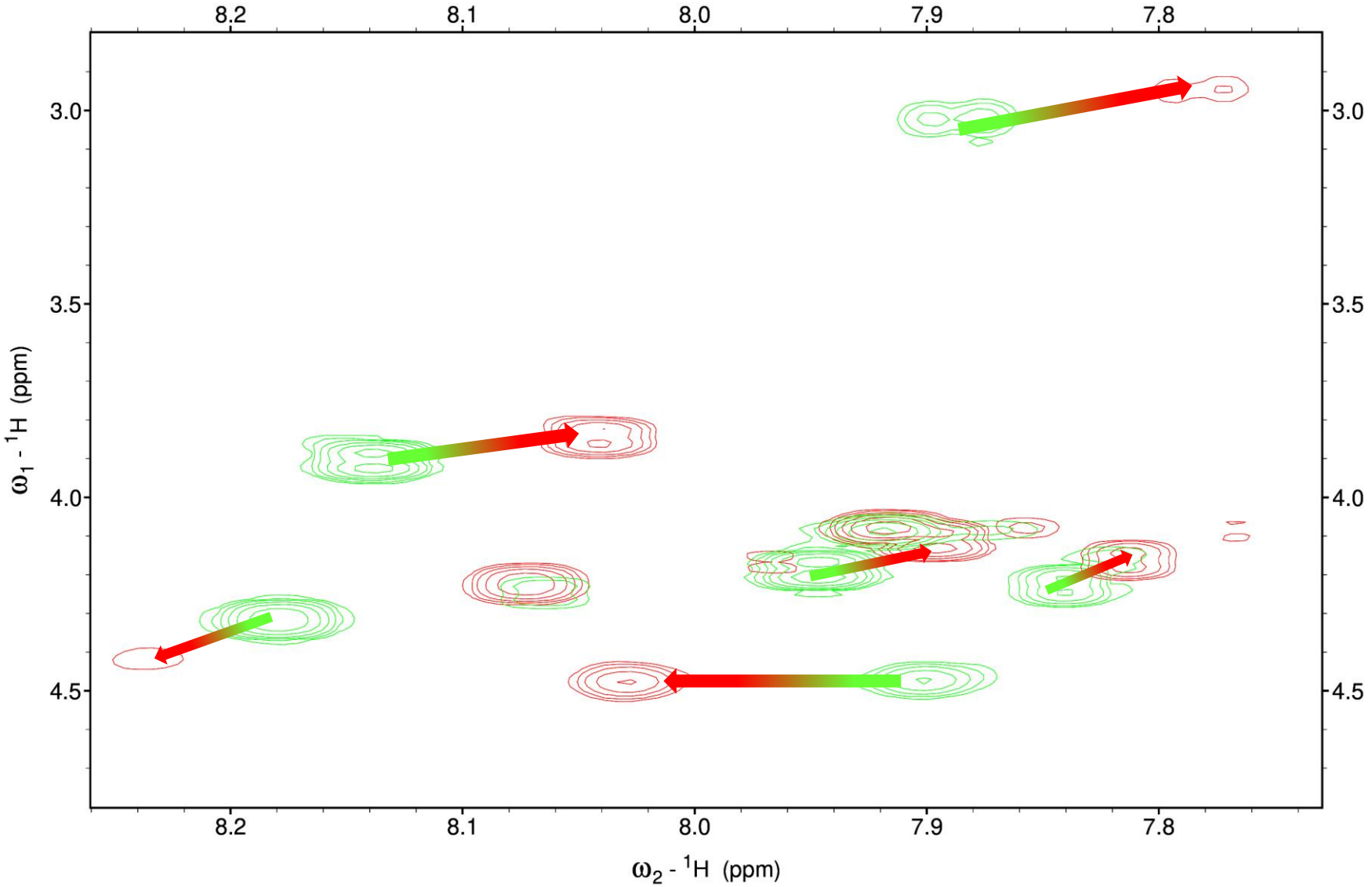
Leuprorelin



Permeability enhancers were screened using 2D NMR

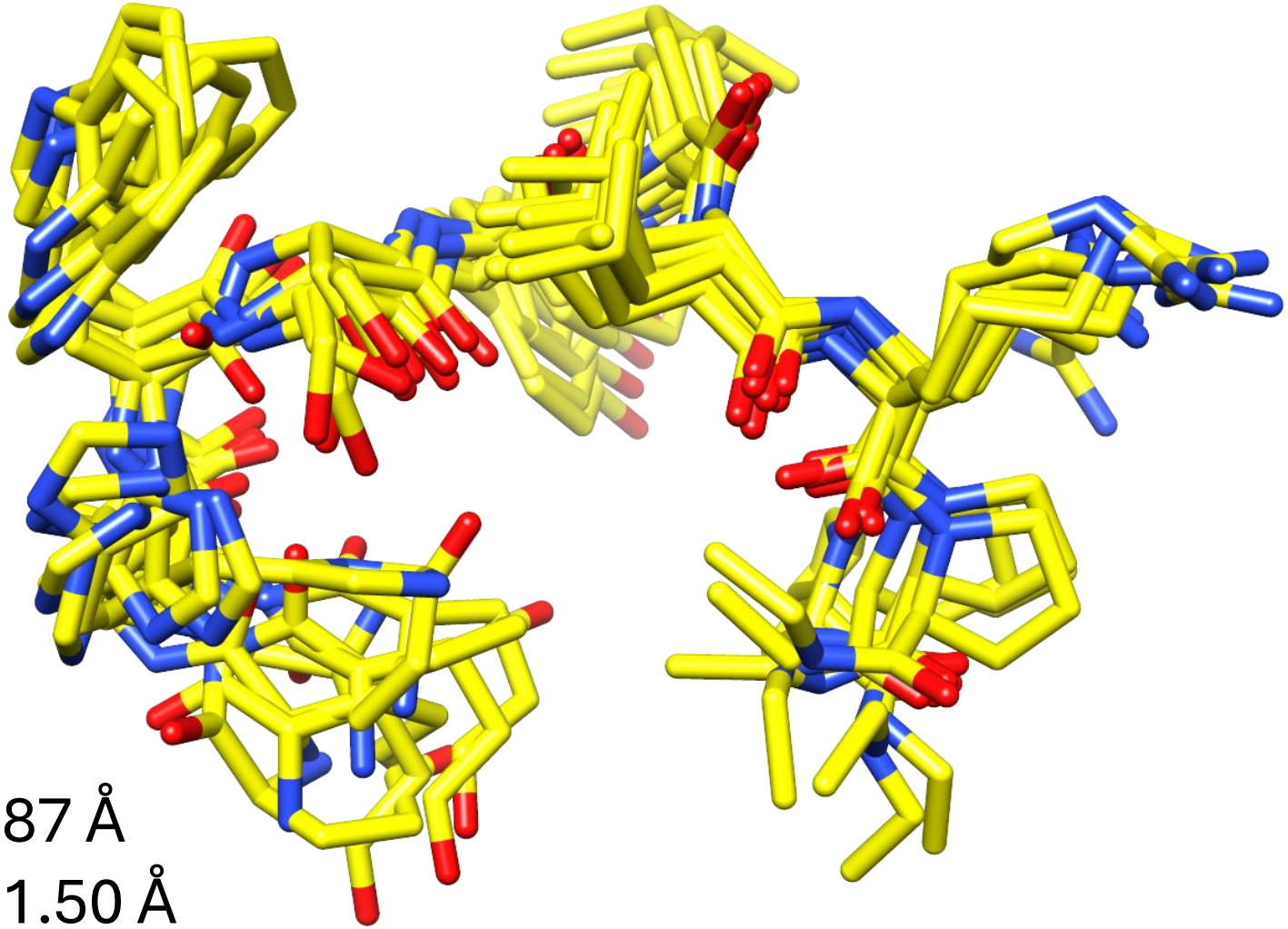


PE1 bound leuprorelin strongly by HN and Hα $\Delta\delta_{1H}$



	ΔHN	ΔHA
pE1	0.008	0.678
H2	0.171	0.154
W3	0.132	-0.016
S4	-0.006	-0.029
Y5	-0.032	-0.094
D-L6	-0.107	-0.082
L7	-0.058	-0.091
R8	-0.115	-0.119
P9		-0.106
	-0.114	-0.079

The structure of the PE1-leuprorelin complex was solved

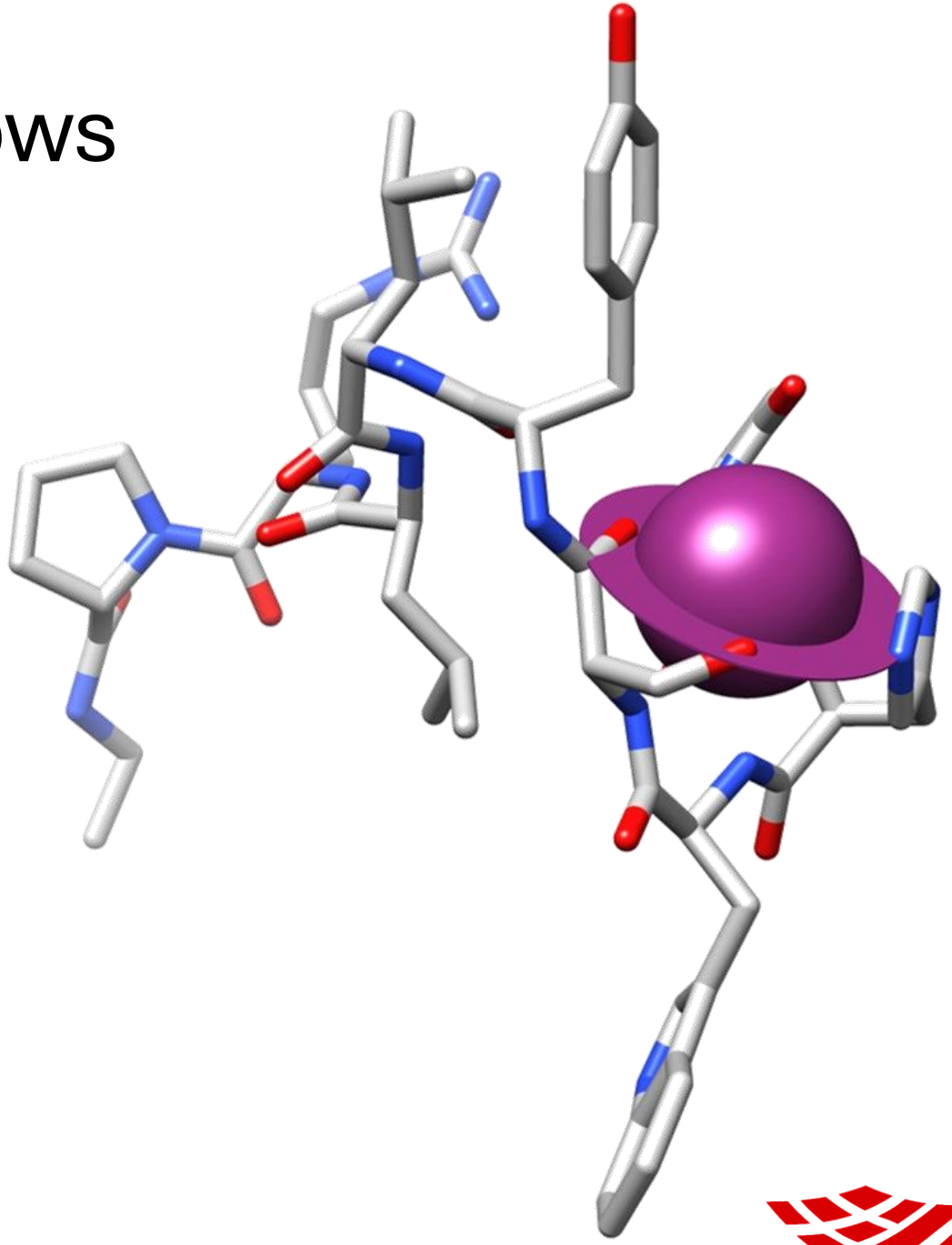


Backbone RMSD 0.87 Å
Heavy atom RMSD 1.50 Å

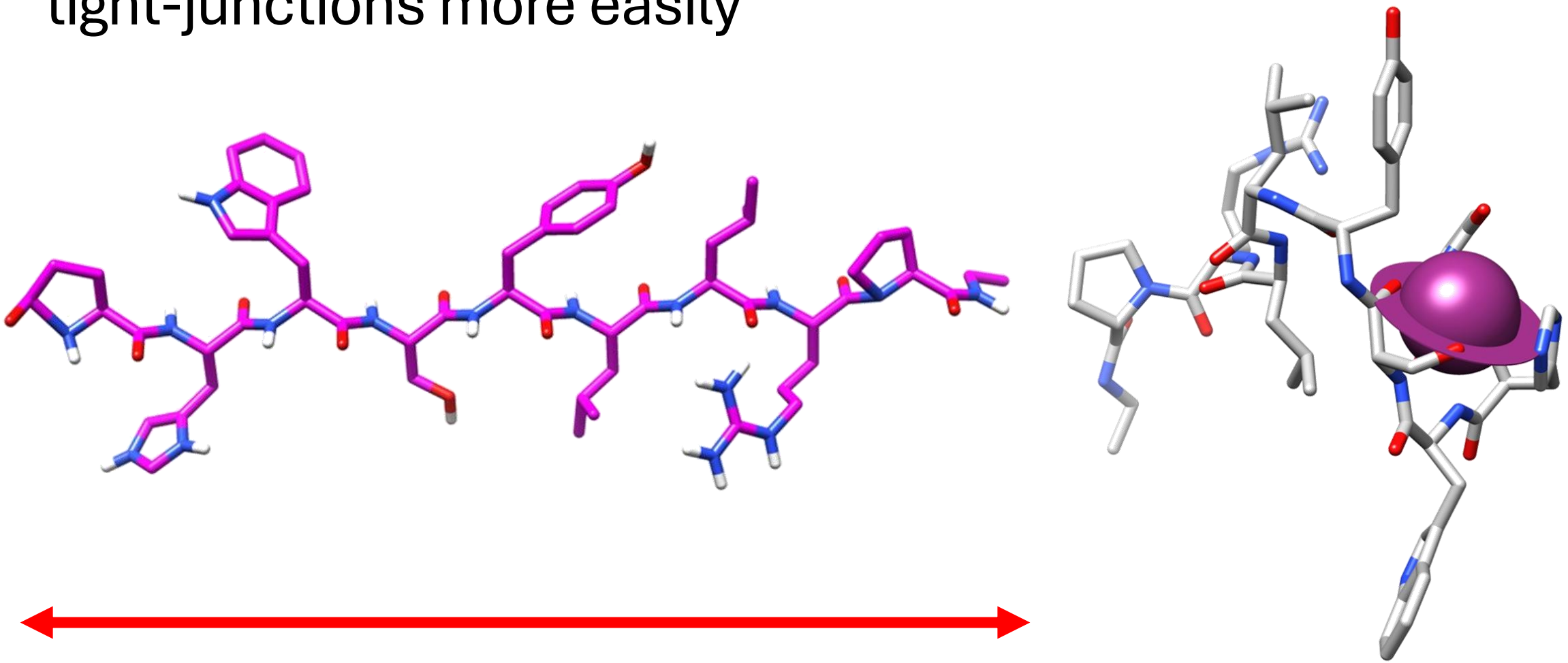
A preliminary NMR structure shows pGlu, His and Ser binding PE1

Binding residues were determined by the degree of chemical shift deviation seen during titration.

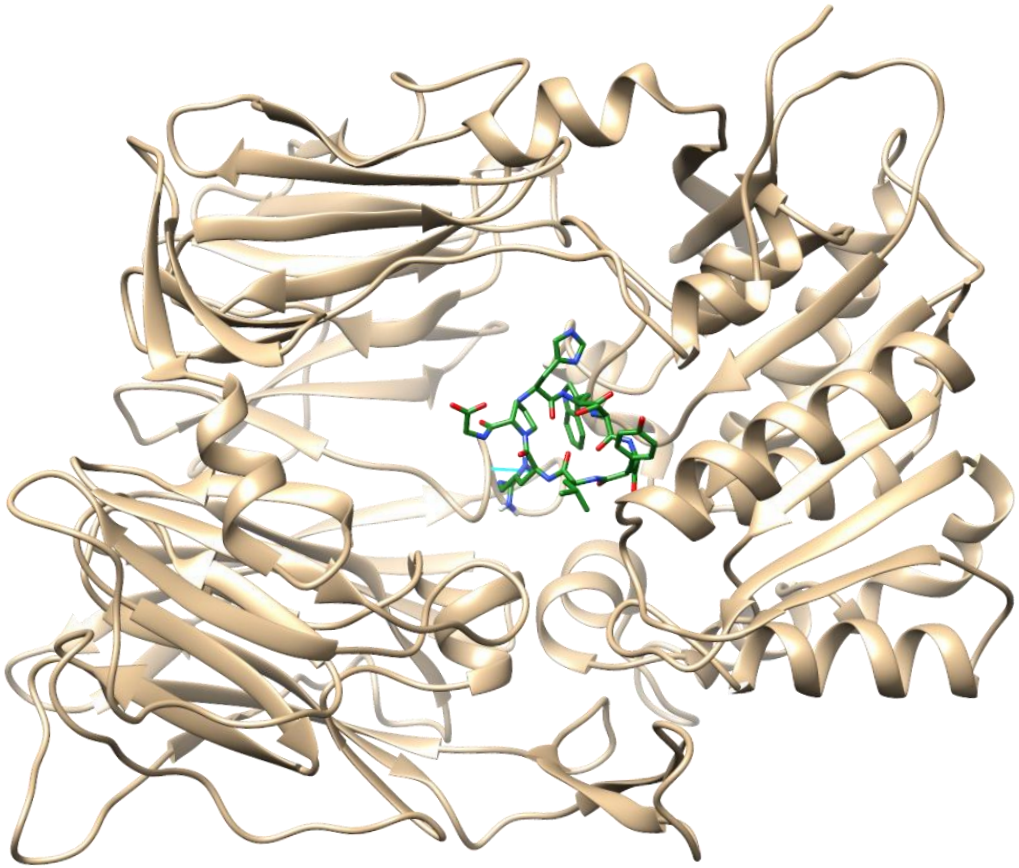
= PE1



The leuprorelin-PE1 complex is smaller and may traverse tight-junctions more easily



AlphaFold2 was used to generate GnRH-enzyme complexes

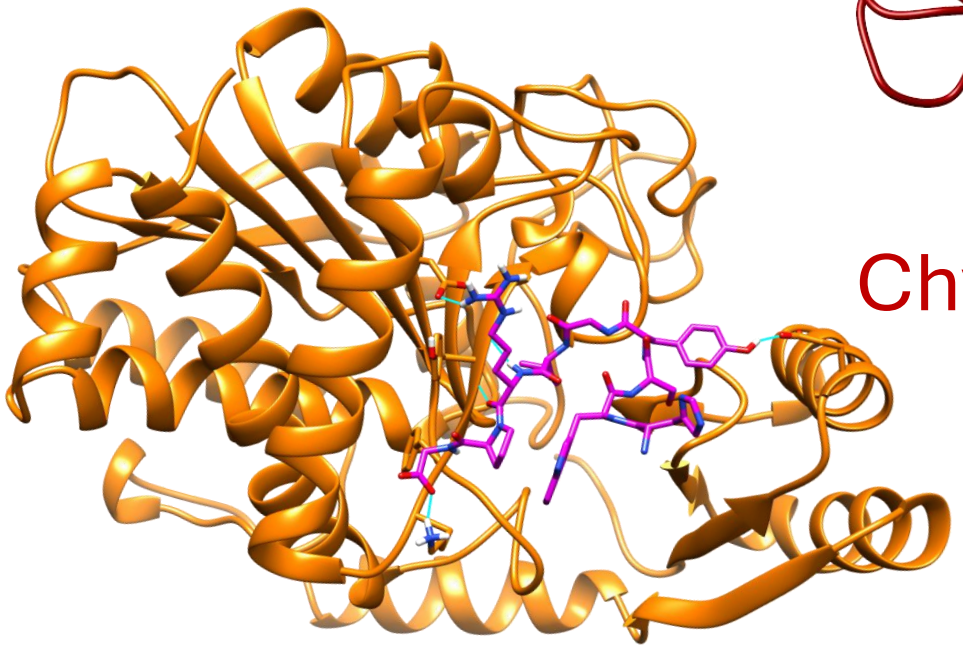


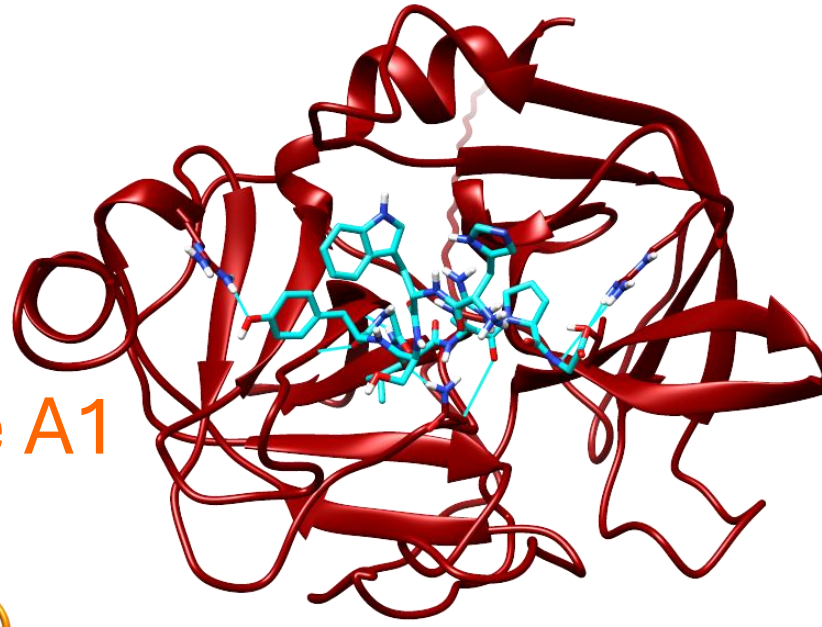
GnRH hormone

Dipeptidyl peptidase

GnRH

Carboxypeptidase A1





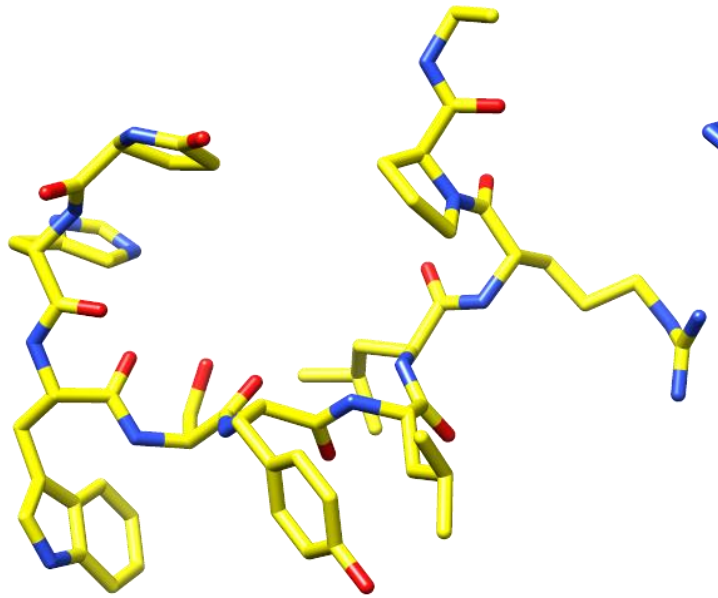
GnRH

Chymotrypsin C

AlphaFold2-multimer on ColabFold (Mirdita, M., Schütze, K., Moriwaki, Y. et al. *Nat Methods* **2022**)

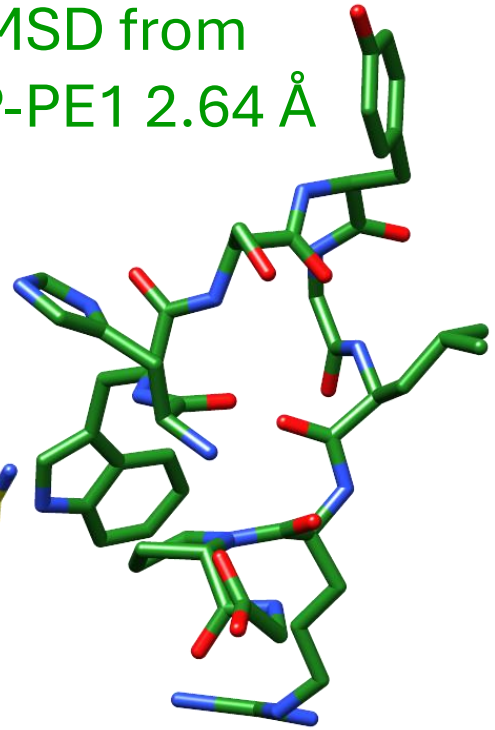
Permeability enhancer complexes render leuprorelin less likely to bind enzymes ➔ Increases their metabolic stability

RMSD LP-PE1 ensemble 0.87 Å



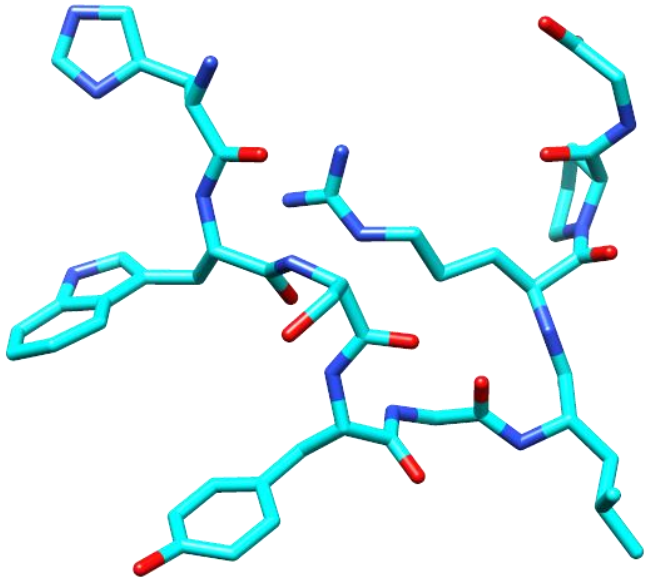
Leuprorelin-PE1 complex from NMR

RMSD from LP-PE1 2.64 Å



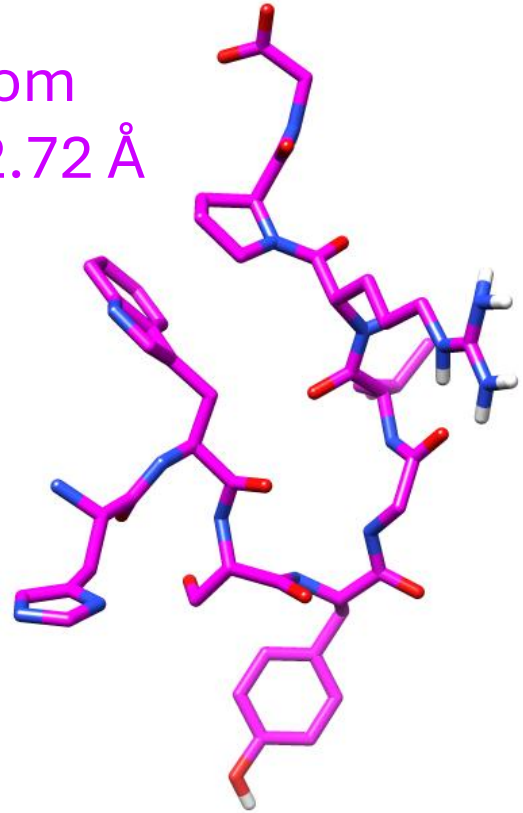
GnRH from AlphaFold complex with dipeptidyl peptidase

RMSD from LP-PE1 2.14 Å



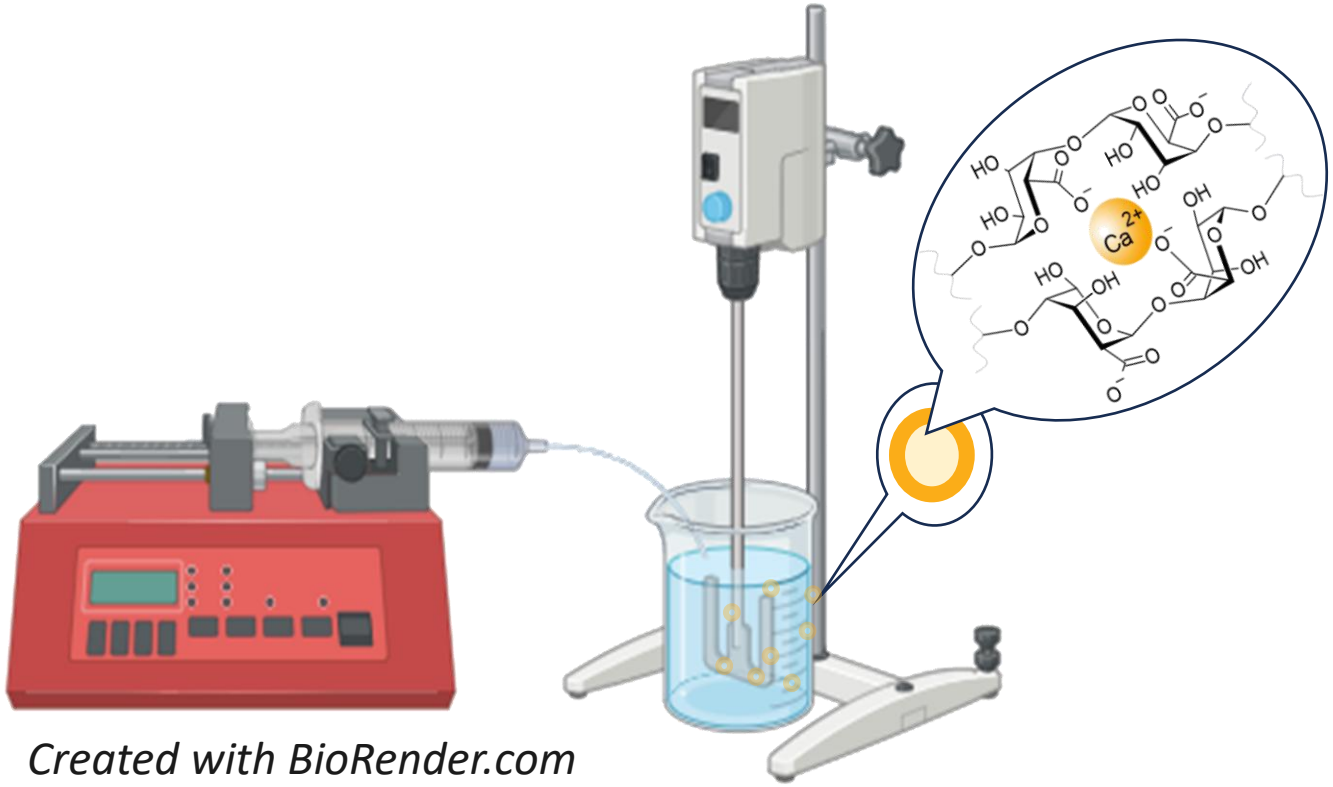
GnRH from AlphaFold complex with chymotrypsin

RMSD from LP-PE1 2.72 Å

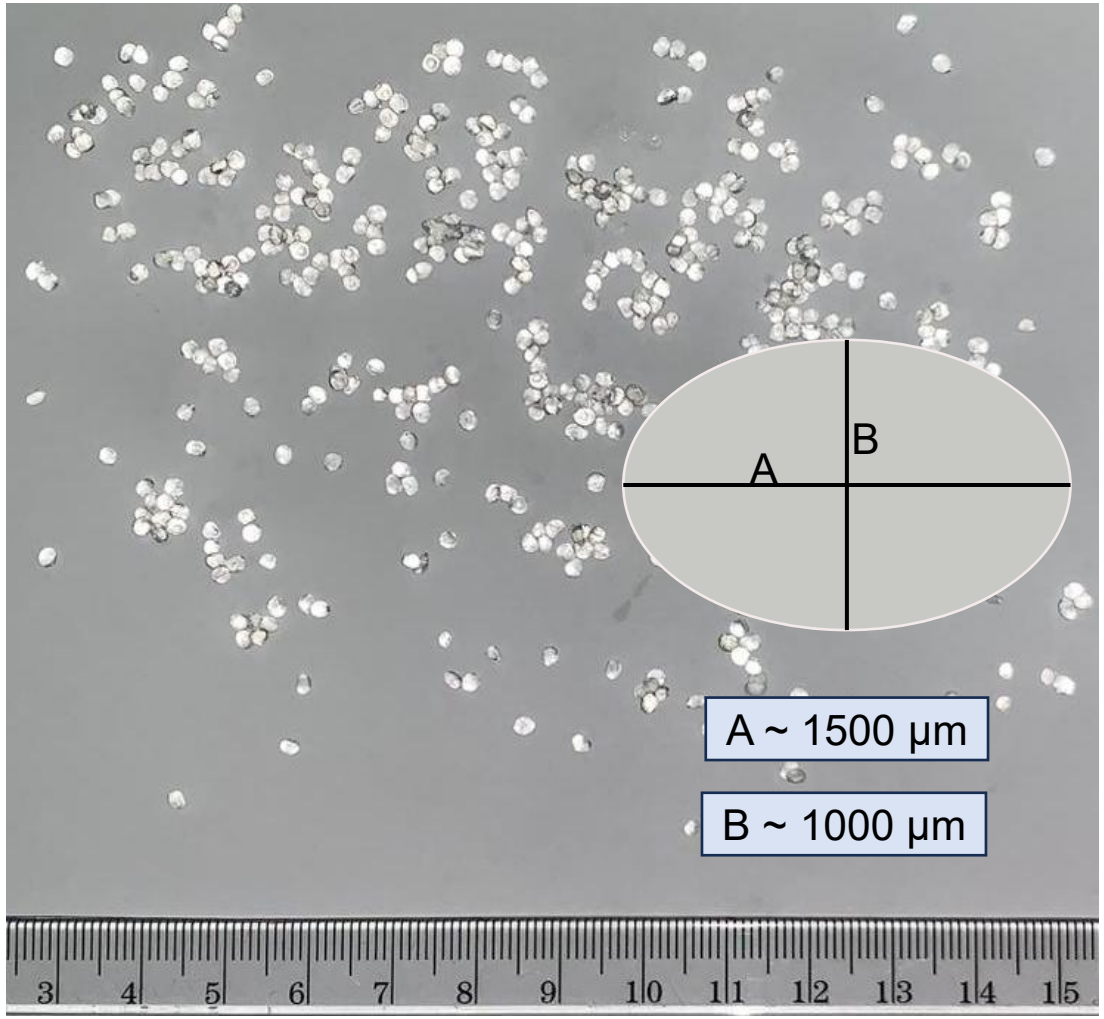


GnRH from AlphaFold complex with carboxypeptidase A1

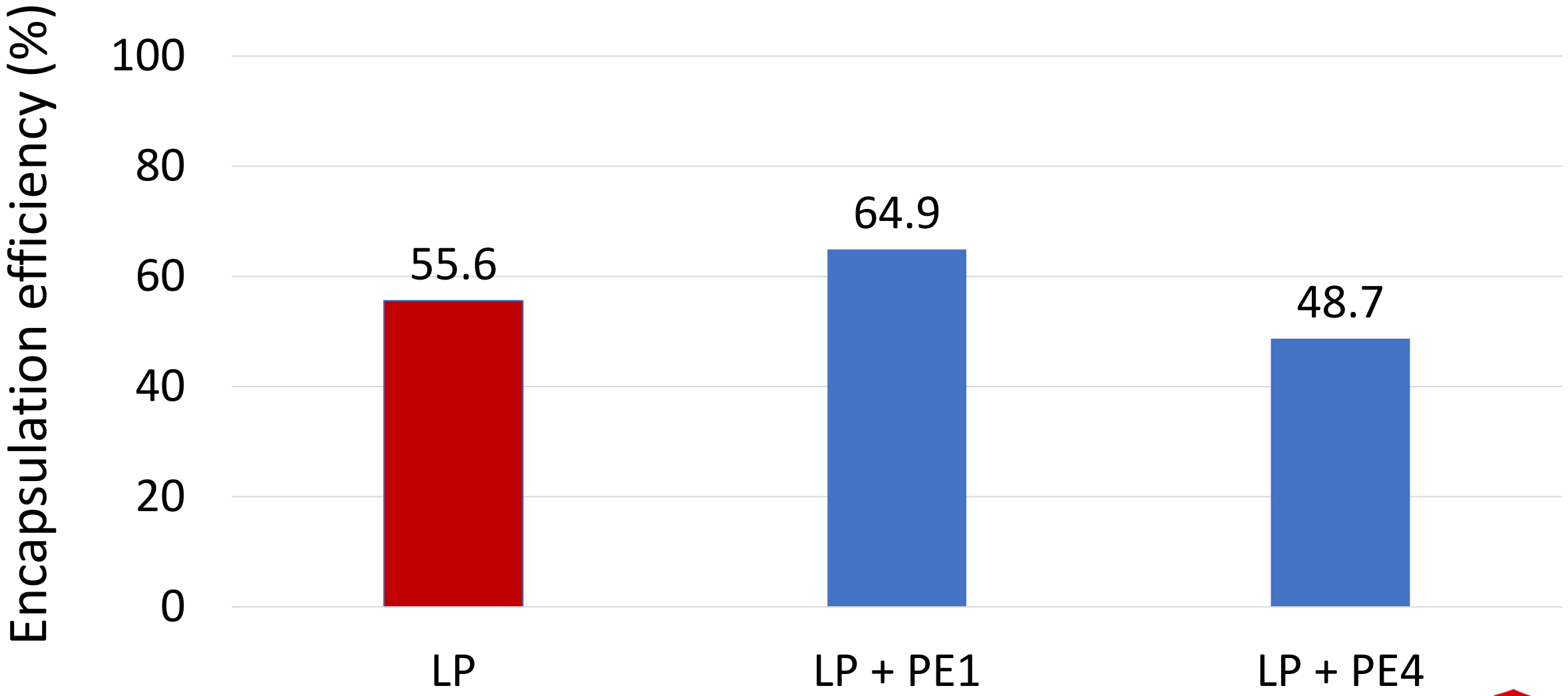
Ca^{2+}-crosslinked alginate microspheres with leuprorelin-permeability enhancer complexes were made



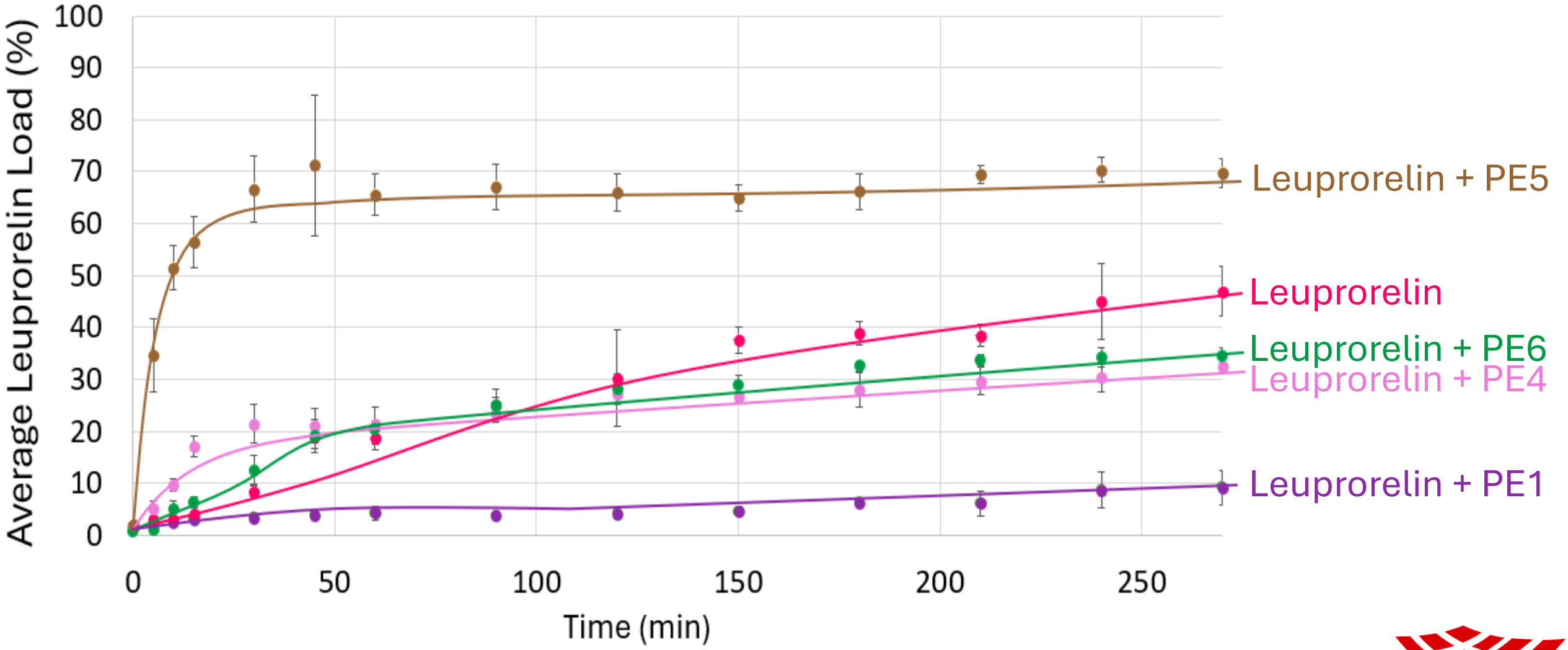
Created with BioRender.com



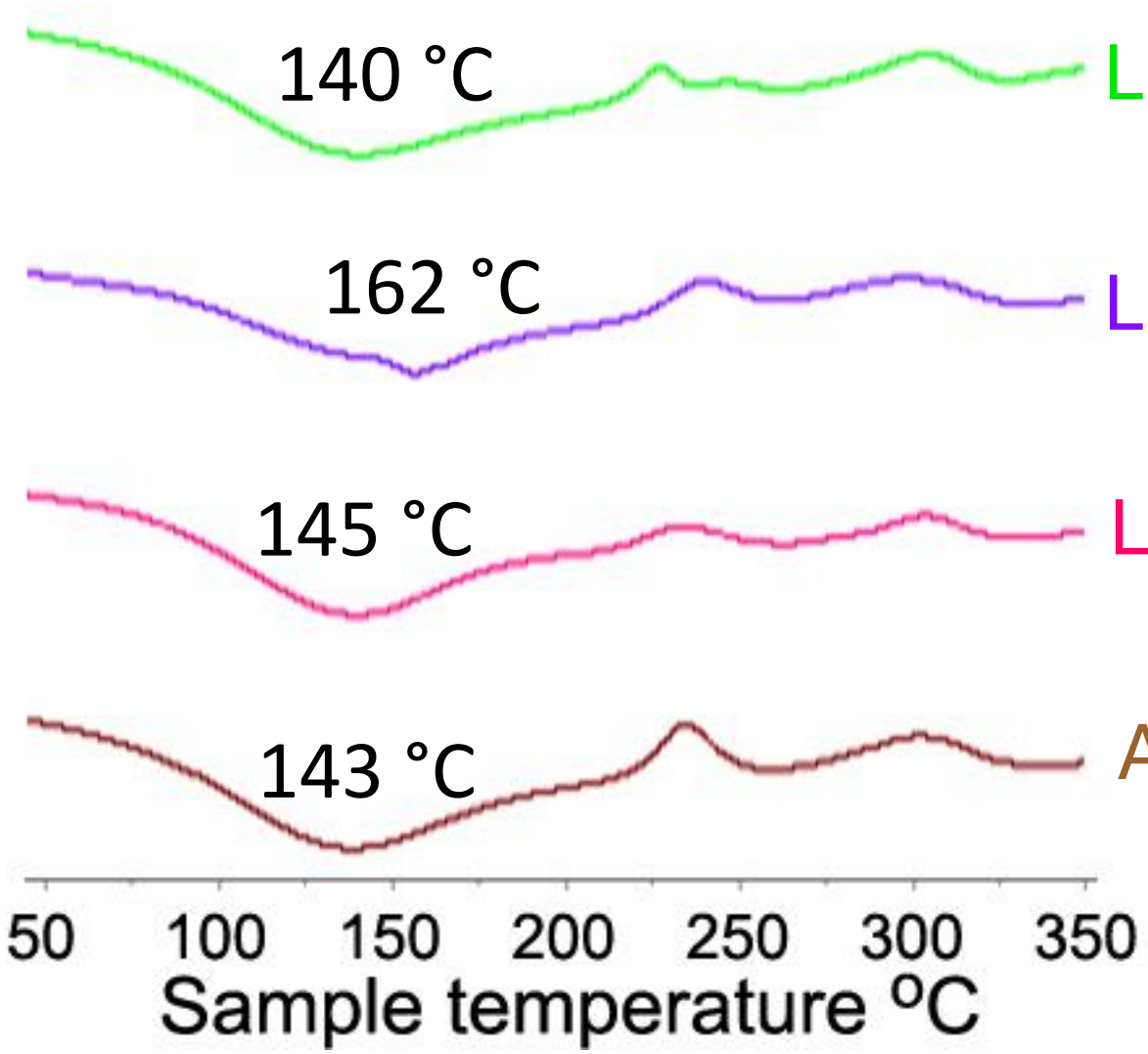
Encapsulation efficiencies were moderate.



PE complexes generally extended leuprorelin release – Particularly PE1



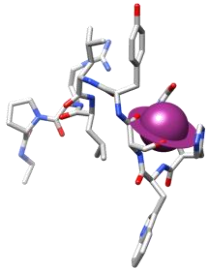
DSC shows microsphere stabilization with PE1



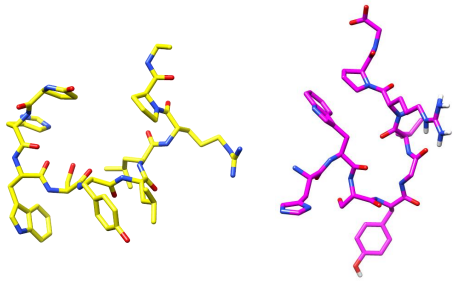
**Leuprorelin melts at 117 °C.*

Summary

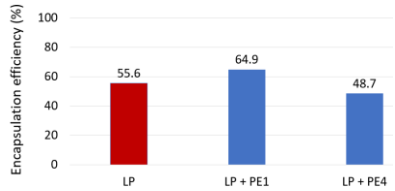
- Leuprorelin complexed permeability enhancers to different degrees.



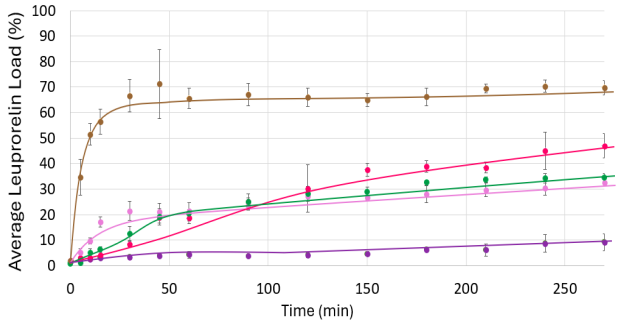
- The structure of PE1-bound leuprorelin differed significantly from GnRH bound in enzymes.



- The encapsulation efficiencies were moderate.



- Release is extended for PE1-bound leuprorelin relative to leuprorelin alone.



Acknowledgements

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ACD Chemsketch