Large molecule administration by the oral route: challenges and current status

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CRS 2022 Annual Meeting & Expo

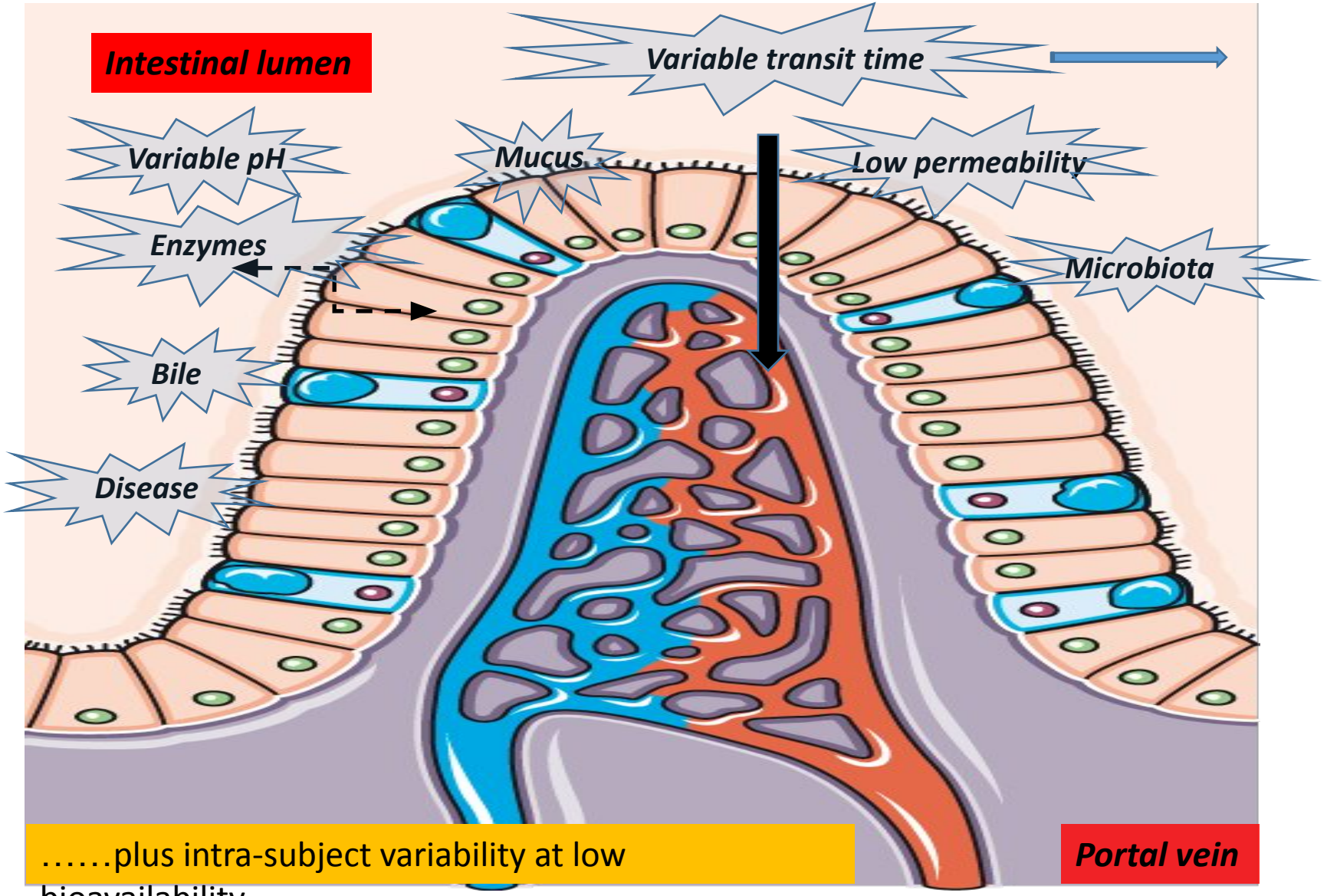
July 11 – 15, 2022 | Montreal Congress Center, Montreal Canada

Advanced Delivery Science

Agenda

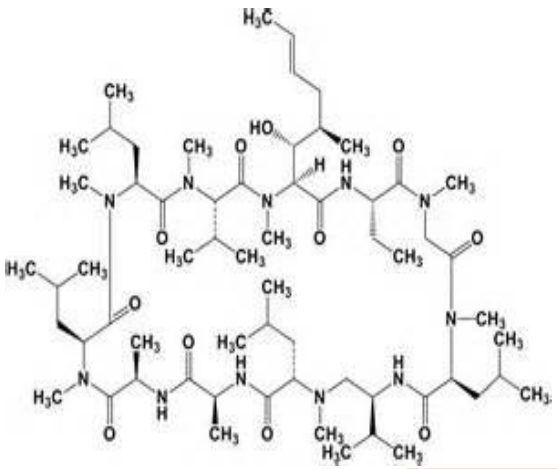
- Important examples of enhancer-based oral macromolecule formulations
- Nanotechnology
- Device options
- New types of payload: dual-acting peptides, PROTACs
- Local delivery alternatives

The problems for macromolecules in the GI tract….



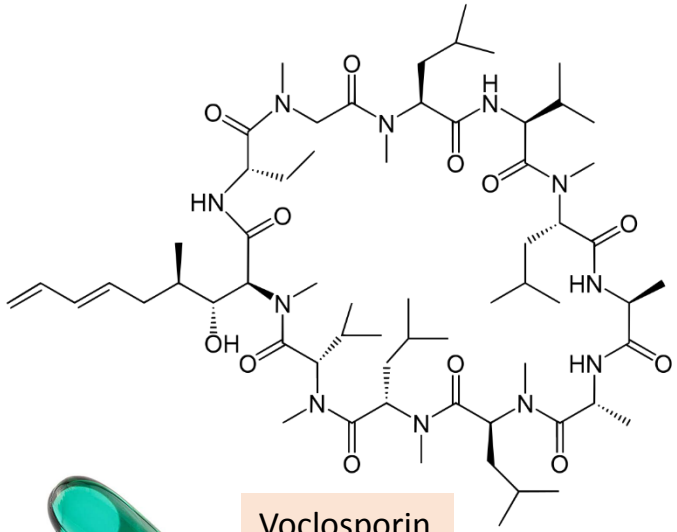
Brayden DJ, et al. (2020). Adv Drug Deliv. Rev. 157:2-36. (Open Access)

The peptide oral formulations approved for systemic delivery



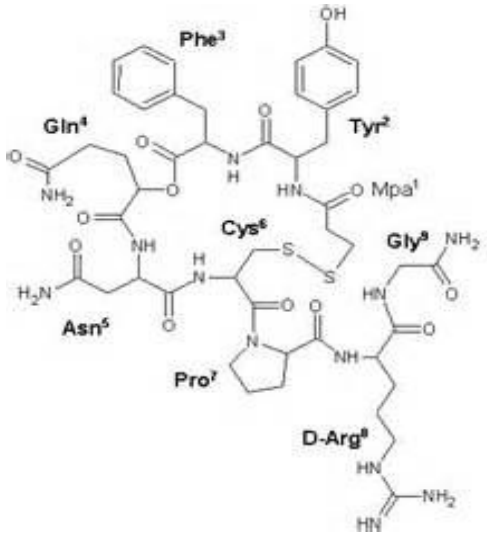
Cyclosporine

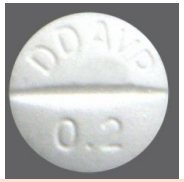
F=40 %



Voclosporin

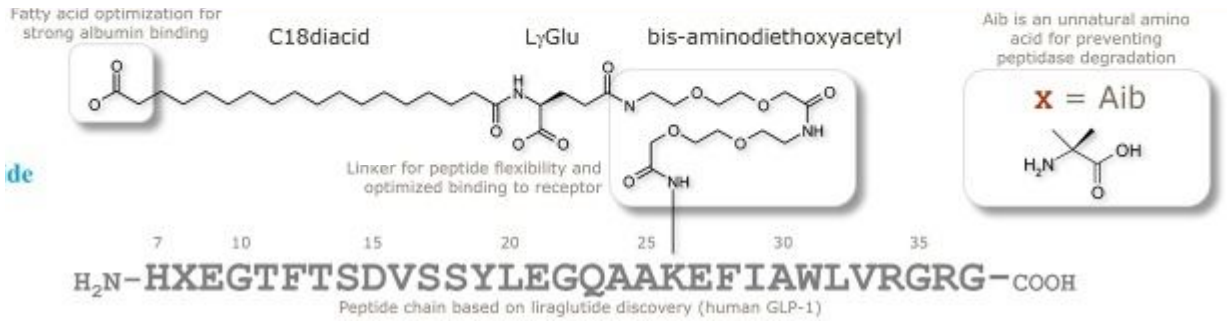
F= 8 -30 %





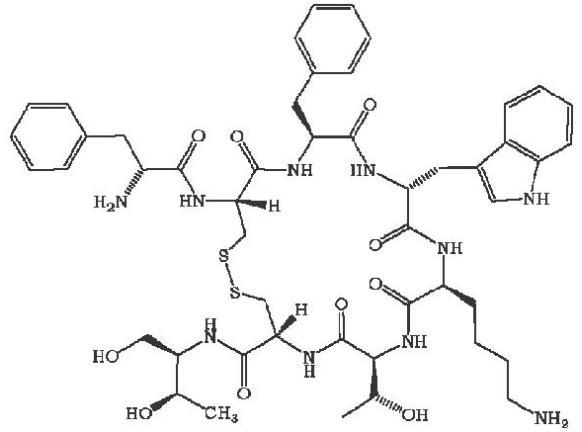
Desmopressin

F=0.2 %



Semaglutide

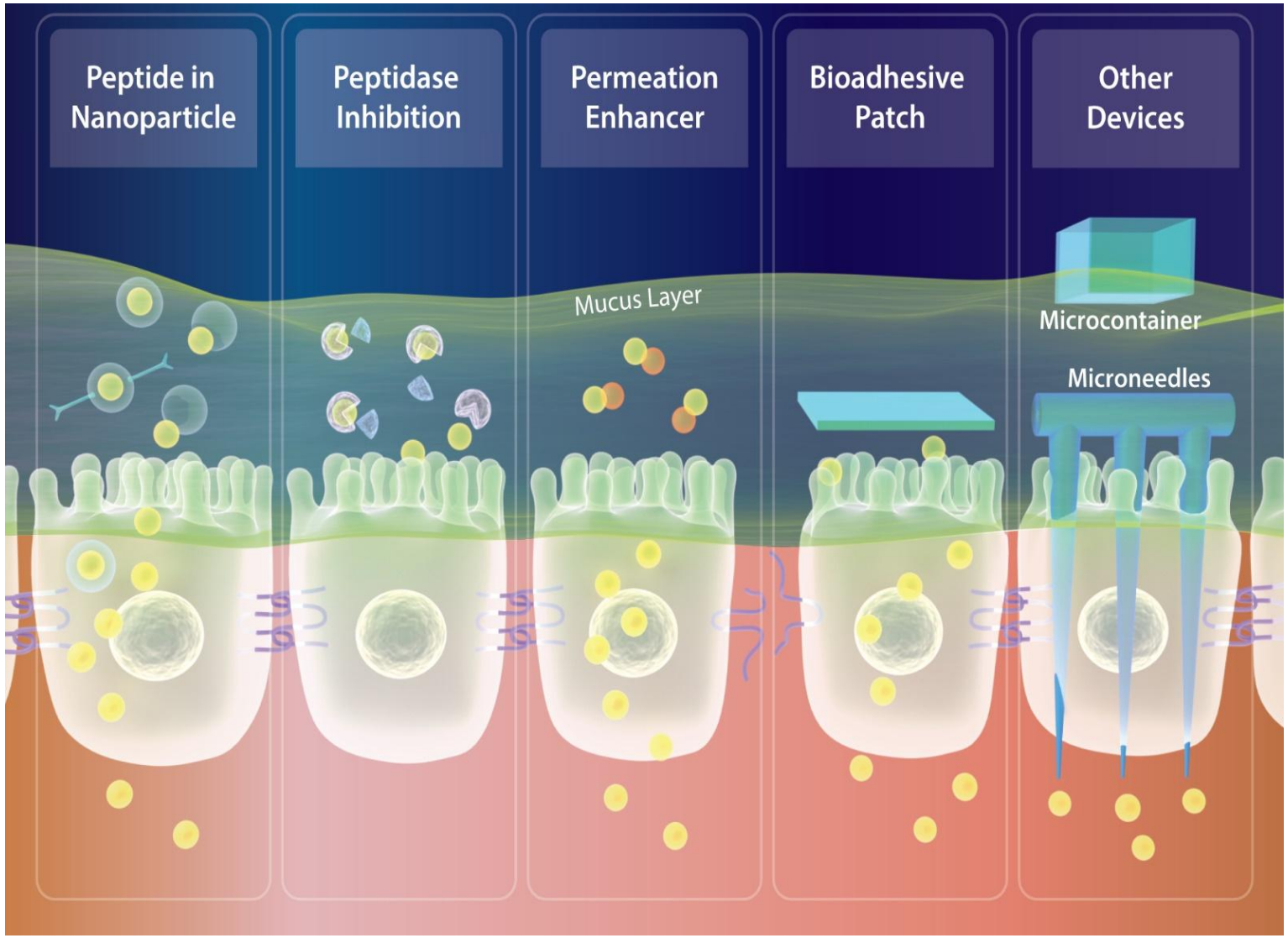
F=0.4-1.0 %



Octreotide

F=0.5-0.8 %

The main delivery strategies to increase the number



Plus
Medicinal chemistry efforts on potency, GI stability, and extension of t½

Brayden DJ, *et al* (2020). Adv Drug Deliv Rev. 157: 2-36 .

Snapshot of enhancer-based systems: approved or in clinical development

Company	Peptide	Technology	Specifics	Phase
Novo-Nordisk	Semaglutide (Rybelsus®)	Eligen™	SNAC	Approved, 2019
Chiasma	Octreotide (Mycapssa®)	Transient Permeability Enhancer (TPE®)	sodium caprylate	Approved, 2020
Osteon	Salmon calcitonin (TBRIA™)	Peptelligence™	Citric acid	III; Not Approved (2016)
Enteris BioPharma	Leuprolide	Peptelligence™	Acyl carnitines / citric acid	II; Ongoing, 2021
Novo Nordisk	Insulin OI338	GIPET™	Sodium caprate	II; terminated (2018)
Oramed	Insulin (ORMD-0801)	POD™	Bile salts and EDTA	IIb; Completed
Biocon	Insulin Tregopil (formerly IN-105)	Acylated PEG-insulin conjugate	Sodium caprate	II; Revised
EnteraBio	PTH (1-34) (EB613)	Eligen™, protease inhibitor	SNAC, Soybean trypsin inhibitor	Phase II completed (2021)

RYBELSUS®
semaglutide tablets

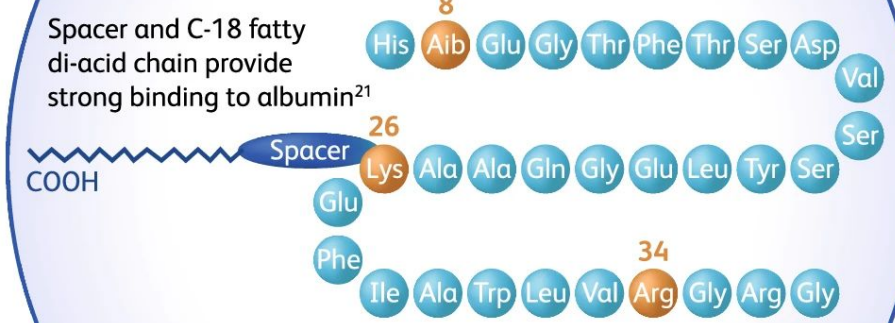
novo nordisk®

Semaglutide is a GLP-1 analog with 94 % homology to human GLP-1[21]

It has a plasma half-life of ~1 week[26]

Amino acid substitution protects against DPP-4 degradation[21]

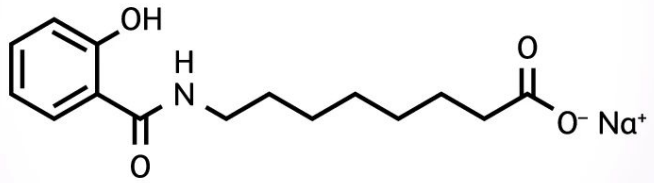
Spacer and C-18 fatty di-acid chain provide strong binding to albumin[21]



Amino acid substitution prevents C-18 fatty acid binding at wrong site[21]

SNAC is a fatty acid derivative that acts as an absorption enhancer to enhance the bioavailability of semaglutide when administered orally[25]

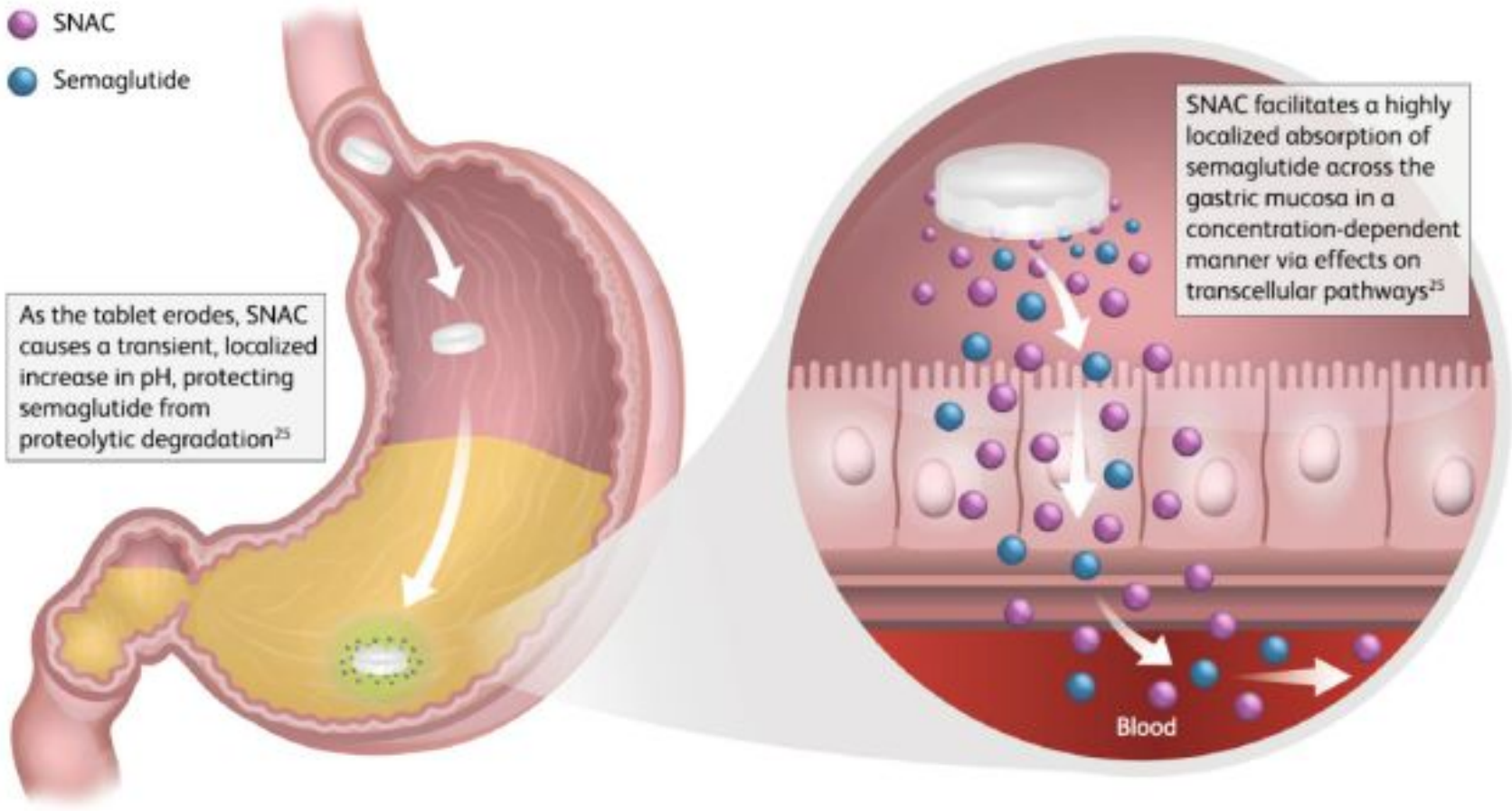
Sodium **N**-(8-[2-hydroxybenzoyl] **A**mino) **C**aprylate



Oral semaglutide is a co-formulation of the GLP-1RA, semaglutide, with an absorption enhancer, SNAC

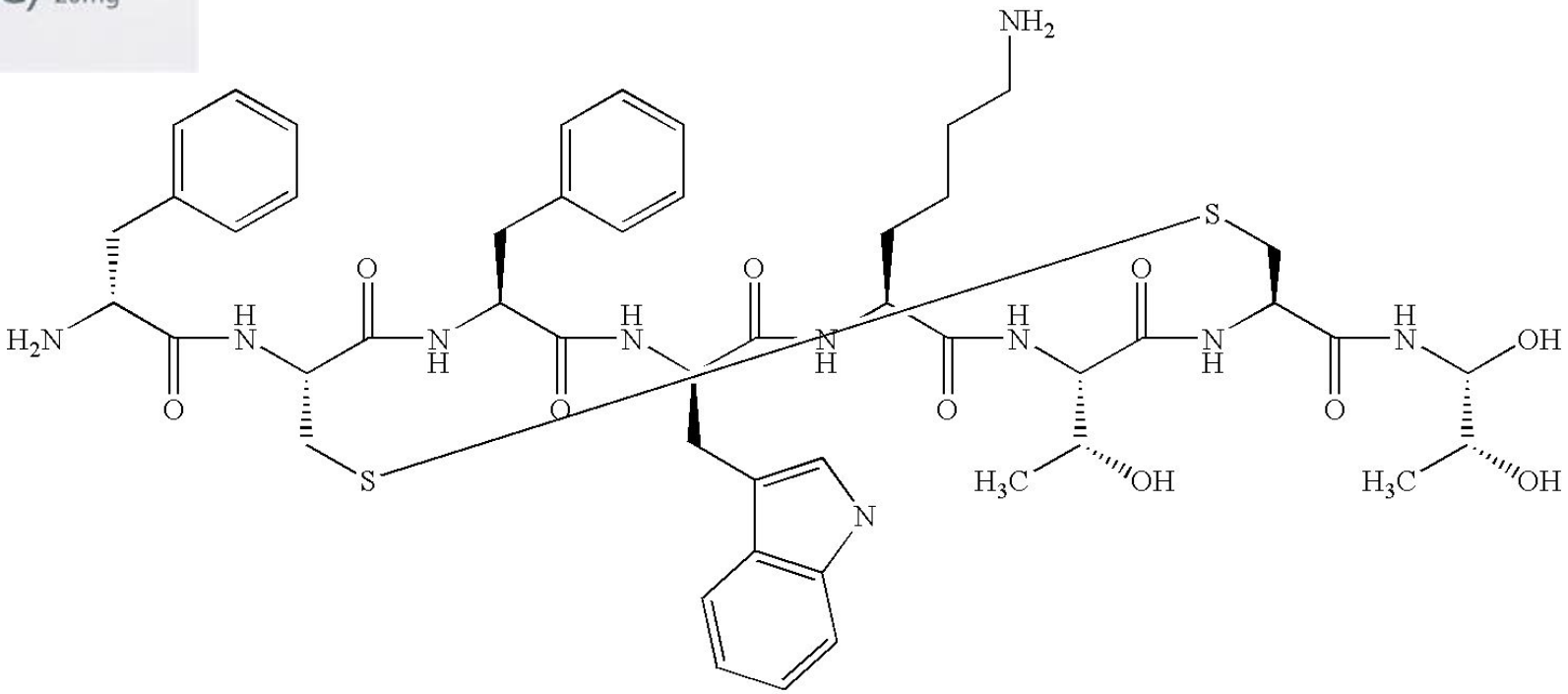
Andersen A, et al (2021) 81(9):1003-1030. doi: 10.1007/s40265-021-01499

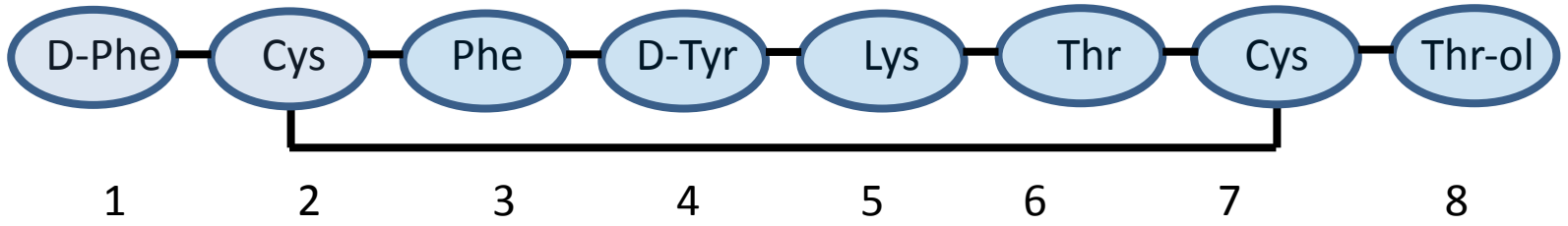
SNAC’s gastric mechanism for semaglutide



Andersen A, et al (2021) 81(9):1003-1030. doi: 10.1007/s40265-021-01499-w.

Mycapssa® (octreotide) capsules 20mg

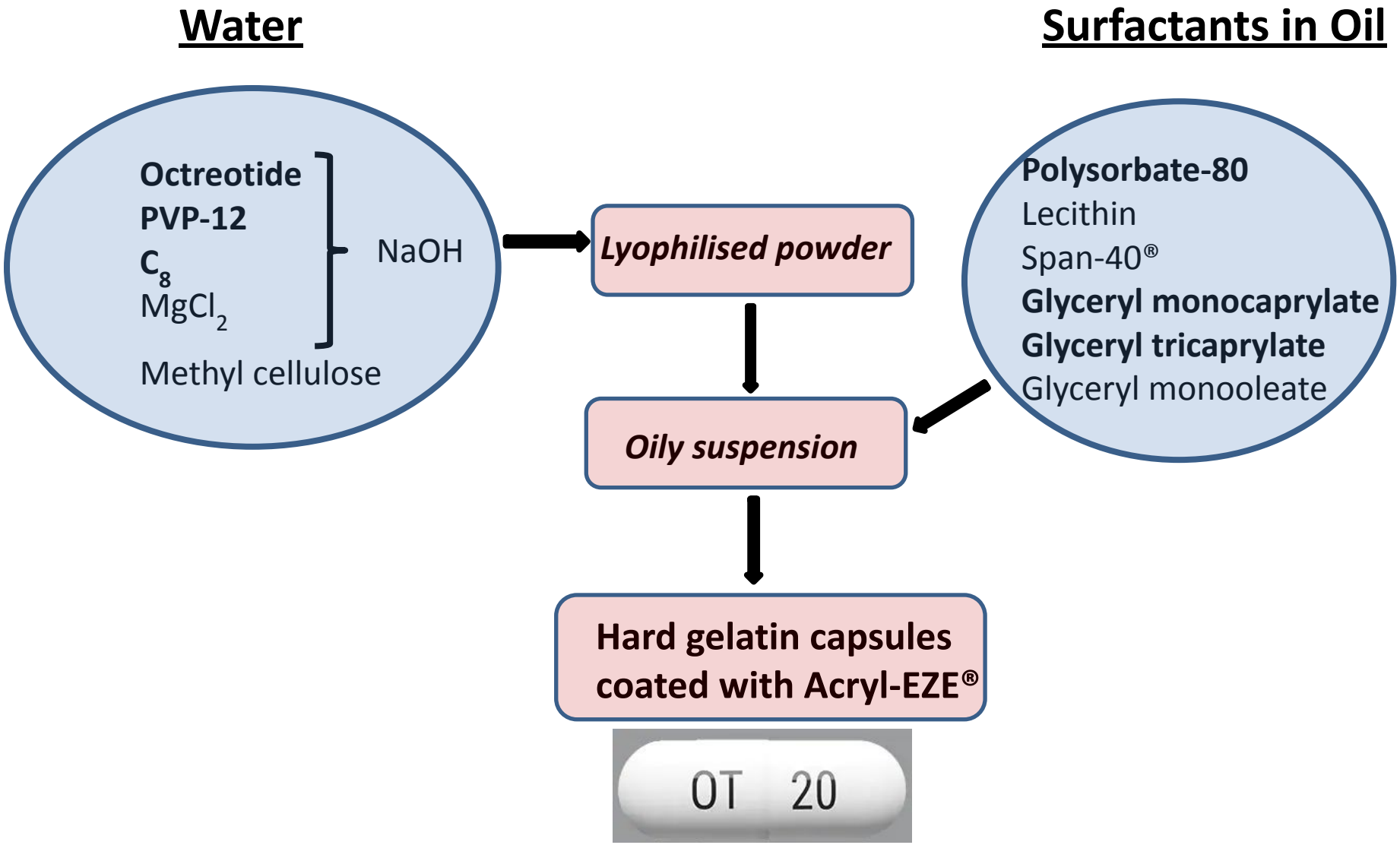




Brayden DJ, Maher S. (2021) Expert Opin Drug Deliv. (10):1501-1512.

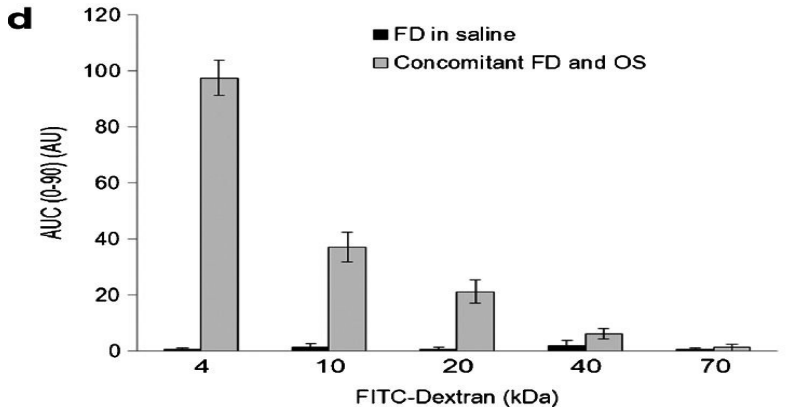
CHIASMA®

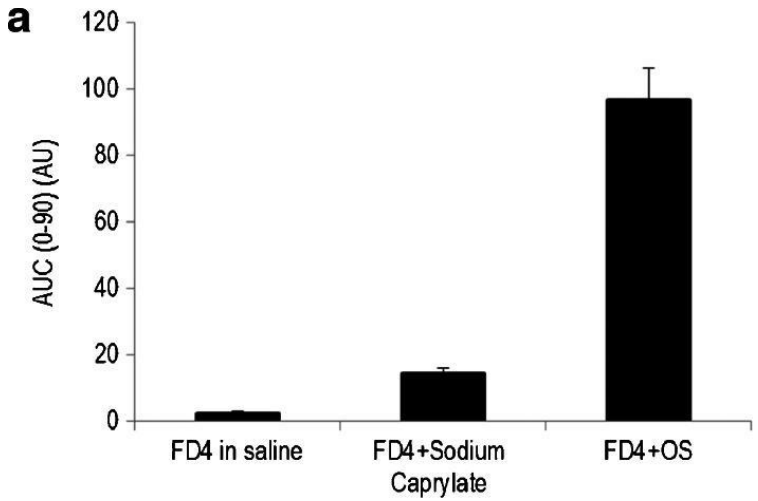
Mycappsa® formulation

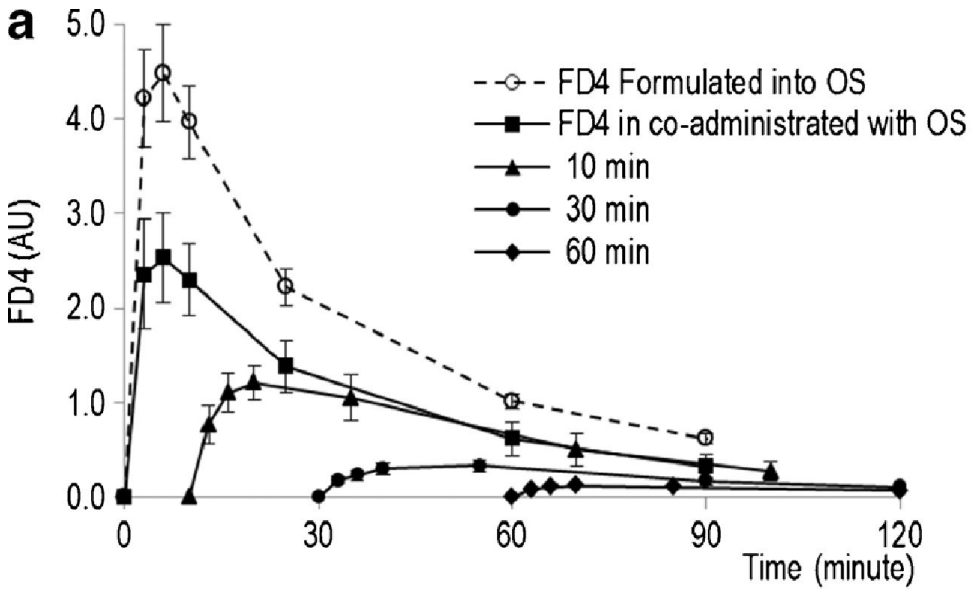


Brayden DJ, Maher S. (2021) Expert Opin Drug Deliv. (10):1501-1512.

Rat i.j. perfusion data revealed the mechanism

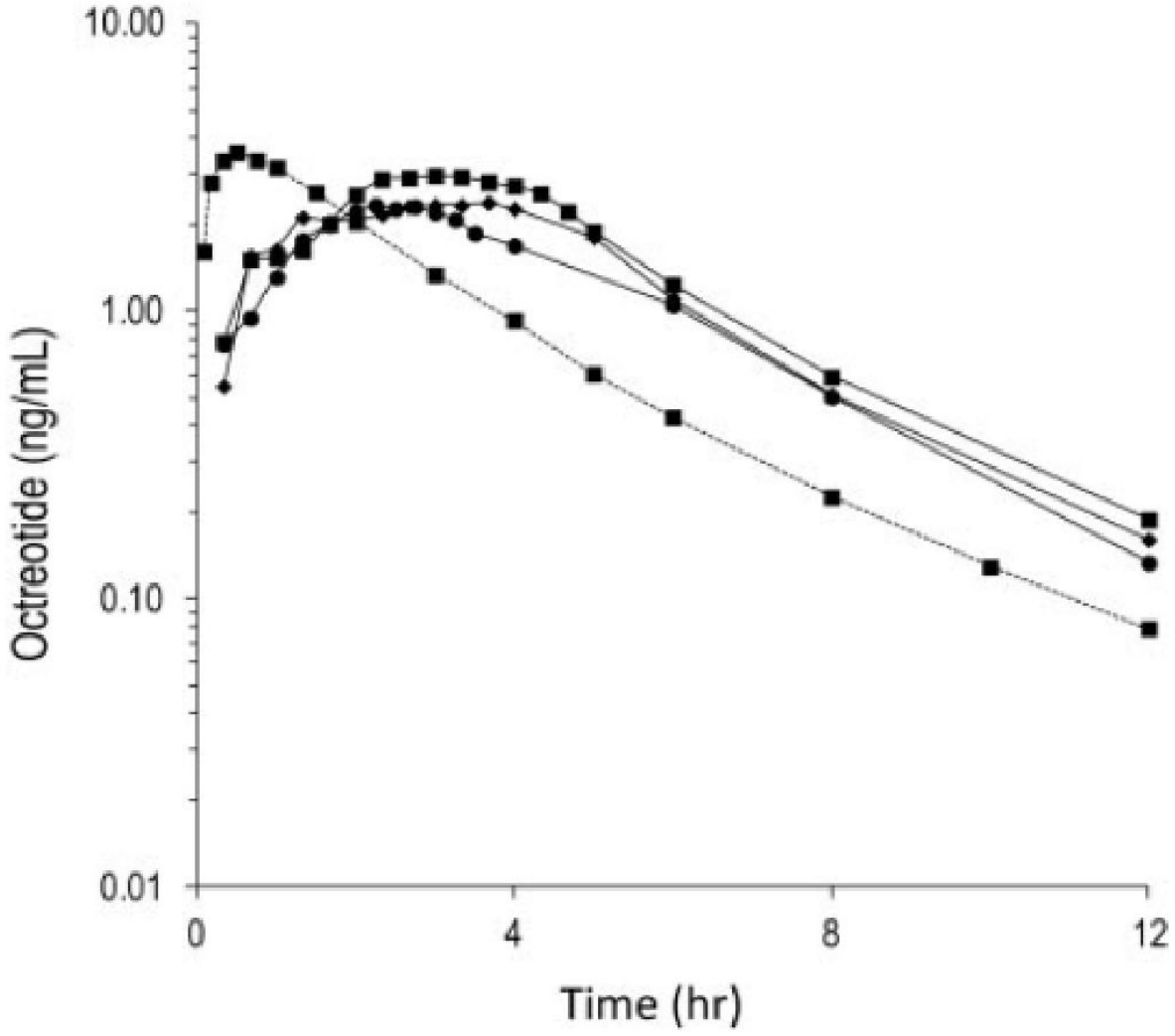






Tuvia S, et al (2014) Pharm Res. ;31(8):2010-21.

Phase 1 trial gave bioavailability of 0.7% for octreotide



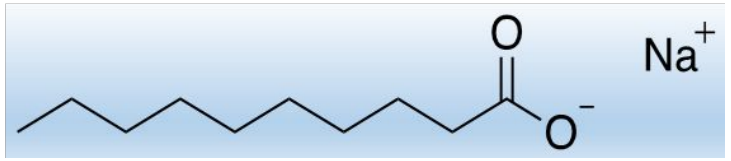
The 20 mg oral octreotide was dosed across three separate studies (n = 12 - 24 subjects per group; ▲, ■, ●). The s.c. comparator dose was 0.1 mg (n = 14; ■ dotted line).

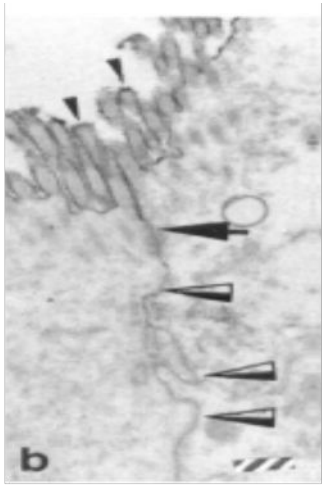
Tuvia S, et al (2012) J Clin Endocrinol Metab. 97(7):2362-9. doi: 10.1210/jc.2012-1179.

C_{10} (sodium caprate)

- Developed as a PE in parallel with SNAC
- History of use in humans
- Up to 3mM in milk
- Good safety profile at EFSA with no upper limit on daily intake
- Not GRAS and never approved in an oral product

Mw: 194 Da, pKa = 5

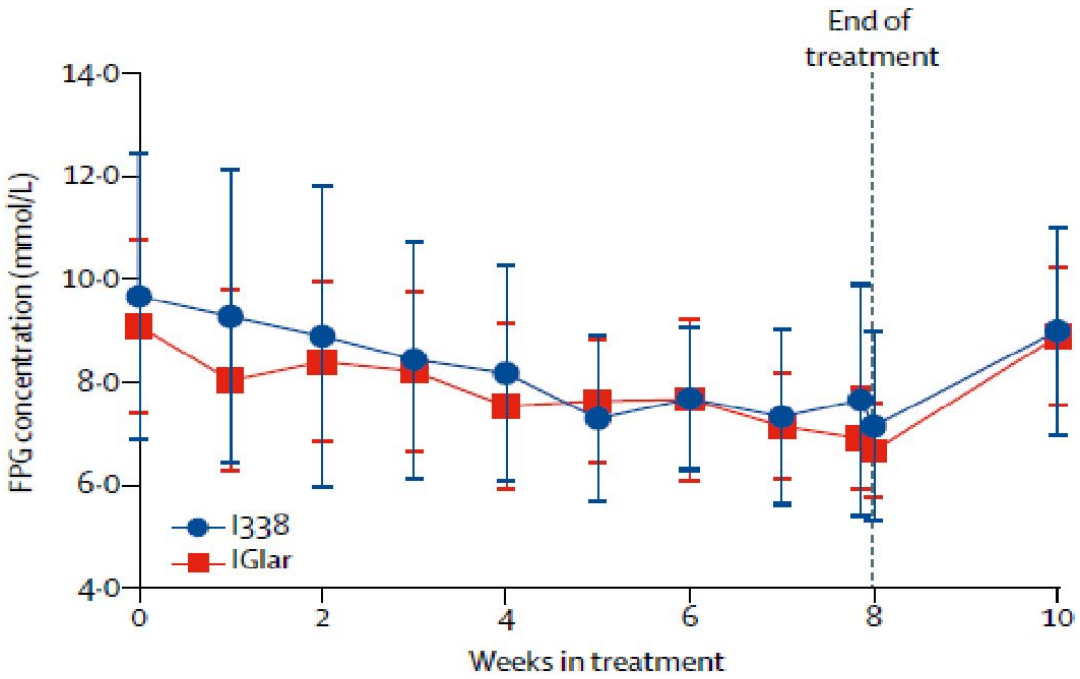




Lindmark, T *et al*. (1998) J. Drug Targeting, 5: 215-223.

merrion pharmaceuticals

Basal insulin I338 (t½=60h): Phase II yielded 2% oral bioavailability

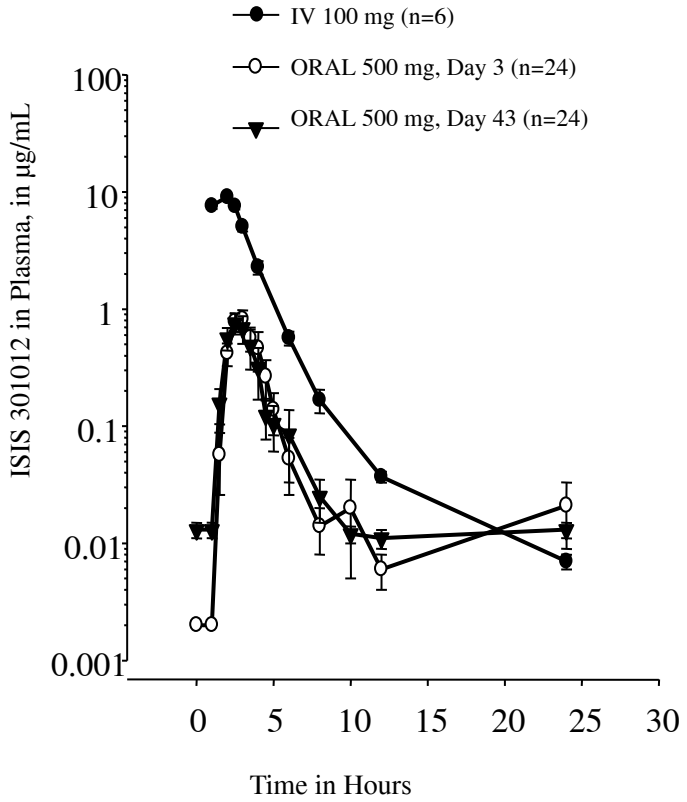


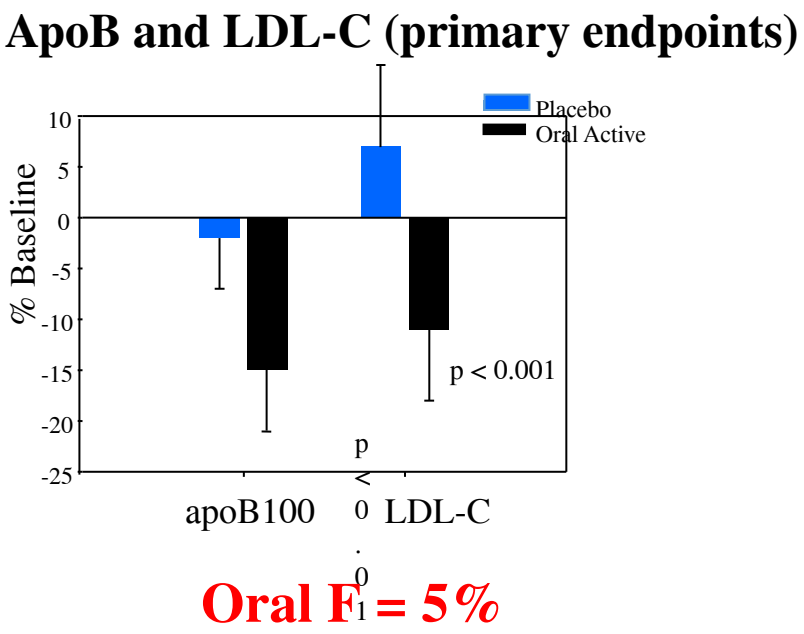
	Least square mean FPG after 8 weeks, mmol/L (95% CI)
I338	7·1 (6·4 to 7·8)
IGlar	6·8 (6·5 to 7·1)

	Estimated mean difference, mmol/L (95% CI)	p value
I338 – IGlar	0·3 (–0·5 to 1·1)	0·46

Halberg, IB *et al*. (2019). Efficacy and safety of oral basal insulin versus insulin glargine in T2D: a randomised double blind Phase II trial. *Lancet Diabetes Endocrinol*. doi: 10.1016/S2213-8587(18)30372-3.

Oral delivery of Ionis 301012 with GIPET®: Phase 1





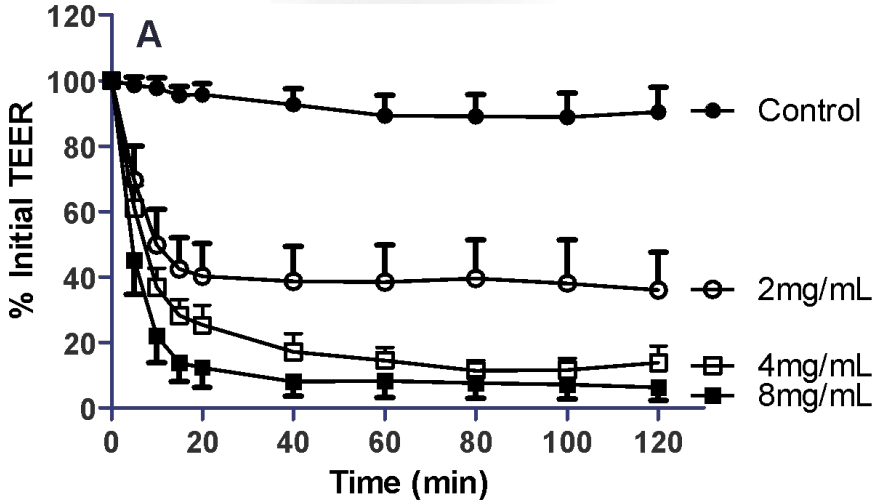
Oral F = 5%

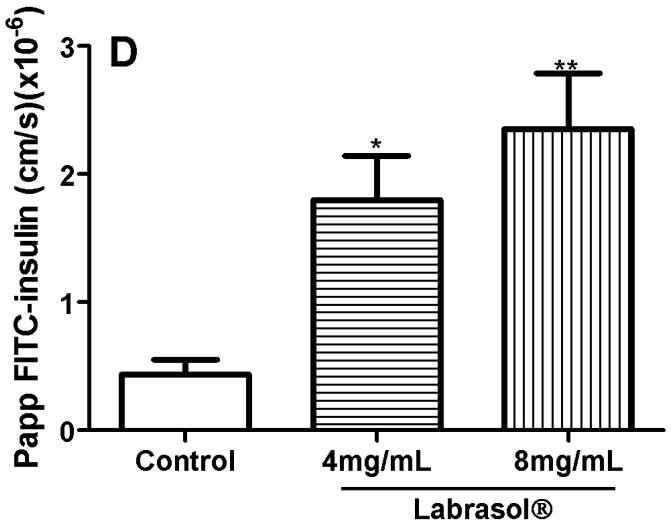
Hardee, GE et al (2008). Chapter 8, Antisense Drug Technology, 2nd Ed. CRC Press.

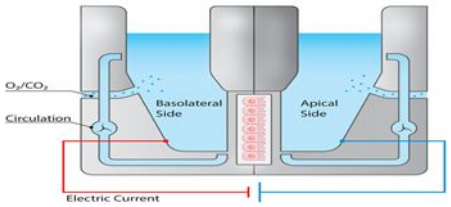
IONIS PHARMACEUTICALS

Other enhancers are being examined with macromolecules

Mono-, di- and triglycerides and mono- and di- fatty acid esters of polyethylene glycol (PEG)-8 and free PEG-8, with caprylic (C_8)- and capric acid (C_{10}) as the main fatty acids.







McCartney F, et al. J Control Release. 2019;310:115-126.

Journal of Medicinal Chemistry

pubs.acs.org/jmc

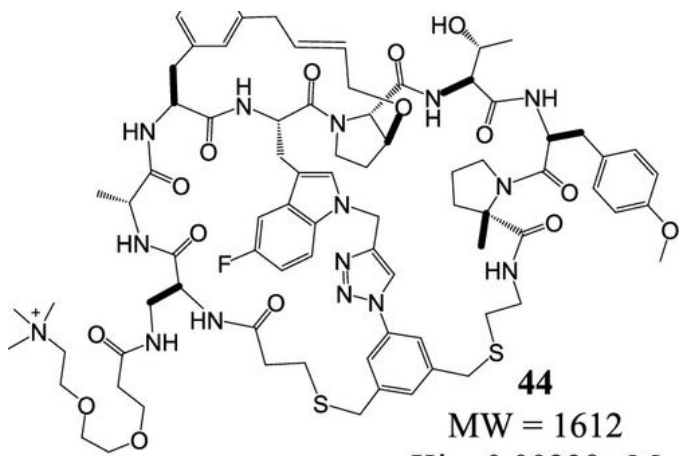
Article

A Series of Novel, Highly Potent, and Orally Bioavailable Next-Generation Tricyclic Peptide PCSK9 Inhibitors

Thomas J. Tucker,* Mark W. Embrey,* Candice Alleyne, Rupesh P. Amin, Alan Bass, Bhavana Bhatt, Elisabetta Bianchi, Danila Branca, Tjerk Bueters, Nicole Buist, Sookhee N. Ha, Mike Hafey, Huaibing He, John Higgins, Douglas G. Johns, Angela D. Kerekes, Kenneth A. Koeplinger, Jeffrey T. Kuethe, Nianyu Li, BethAnn Murphy, Peter Orth, Scott Salowe, Aurash Shahripour, Rodger Tracy, Weixun Wang, Chengwei Wu, Yusheng Xiong, Hratch J. Zokian, Harold B. Wood, and Abbas Walji

Cite This: https://doi.org/10.1021/acs.jmedchem.1c01599

Read Online



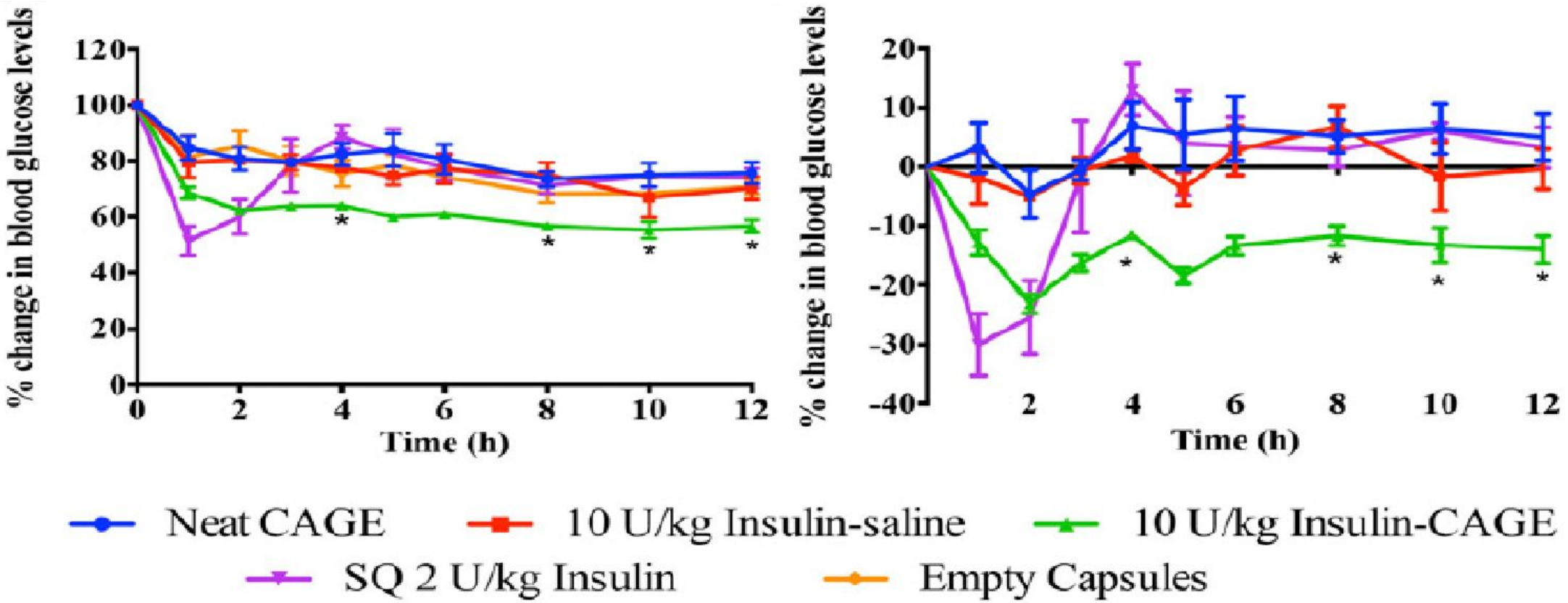
44

MW = 1612

Ki = 0.00239 nM

%F cyno = 2.9

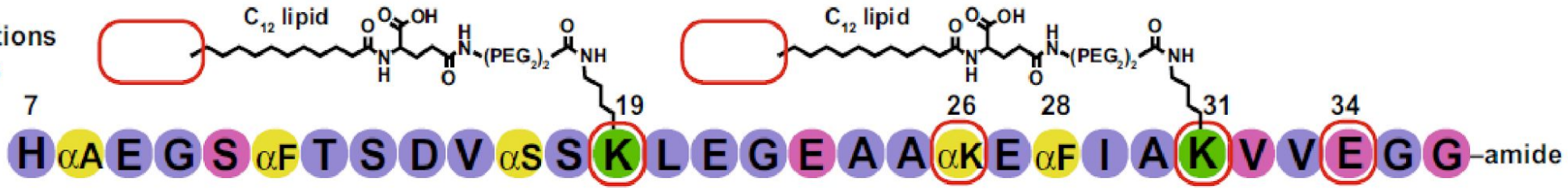
Ionic liquids made from choline and geranic acid "CAGE" (I_{20} Therapeutics)



Banerjee A, et al. Proc Natl Acad Sci U S A. 2018 ;115(28):7296-7301.

Bile salt and propyl gallate combined as PEs

MEDI7219
- 12 amino acid substitutions
- 5 α-methyl amino acids
- Bis-lipidation



	Peptide	
	Semaglutide	MEDI7219
Peptide dose, mg/dog	20	20
PE dose, mg/dog	300 (SNAC)	300 (100 mg NaCDC and 200 mg PG)
Coating	none	pH 5.5 enteric
$t_{½}$, hours	60.5 (13.6)	9.8 (13.2)
T_{max}, hours	2.0 (1.5–2.5)	1.5 (1.0–4.5)
C_{max}, ng/mL	21.1 (72.5)	1,450 (63.2)
$AUC_{0\text{-}inf}$, ng·h/mL	1,440 (45.8)	13,500 (54.2)
F, %	0.08 (45.8)	5.92 (54.2)
CL/F, mL/h	16,000 (47.4)	1,880 (52.1)

Tablets in dogs….

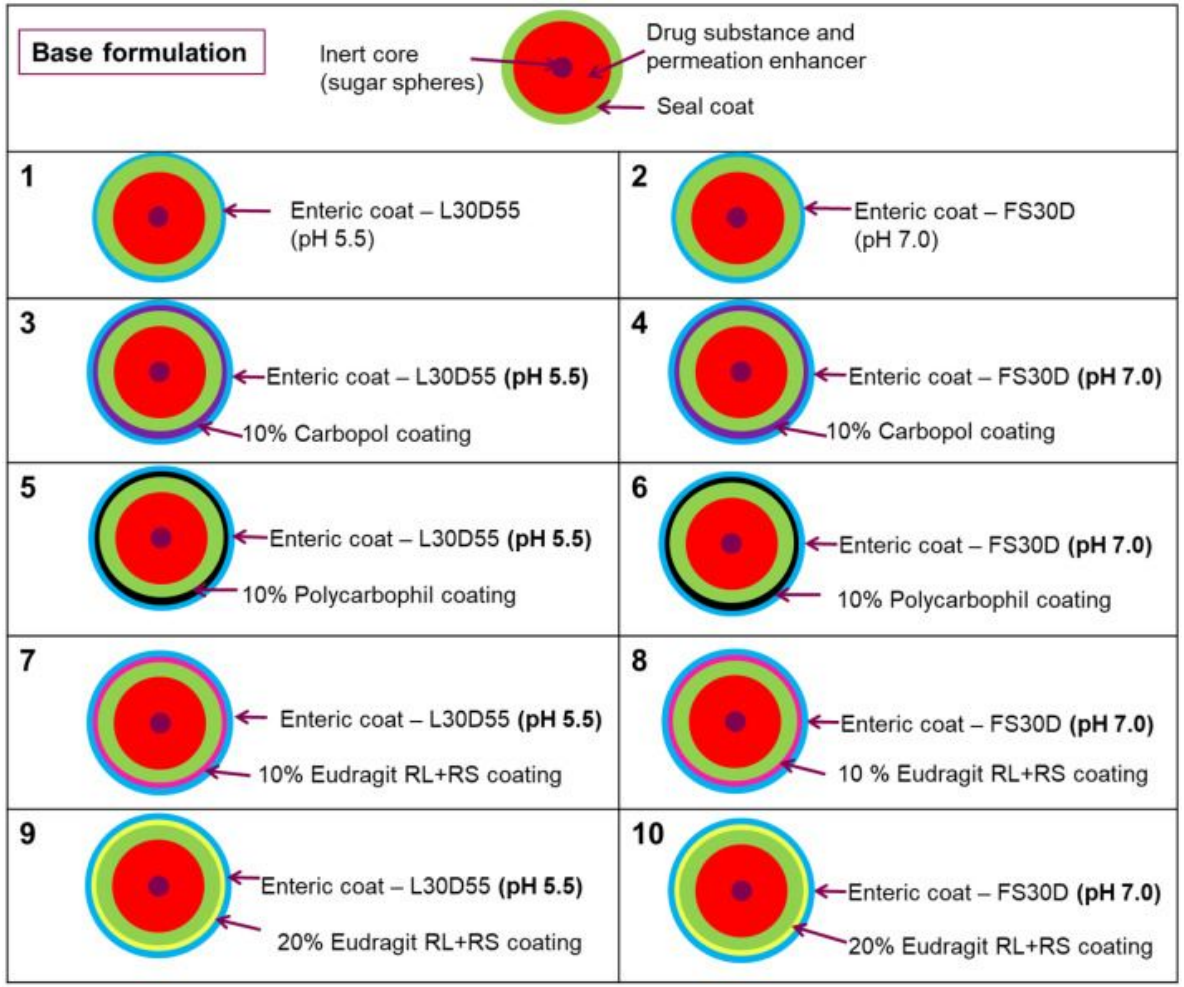
Pechenov S, et al. Sci Rep. 2021):22521. doi: 10.1038/s41598-021-01750-0.

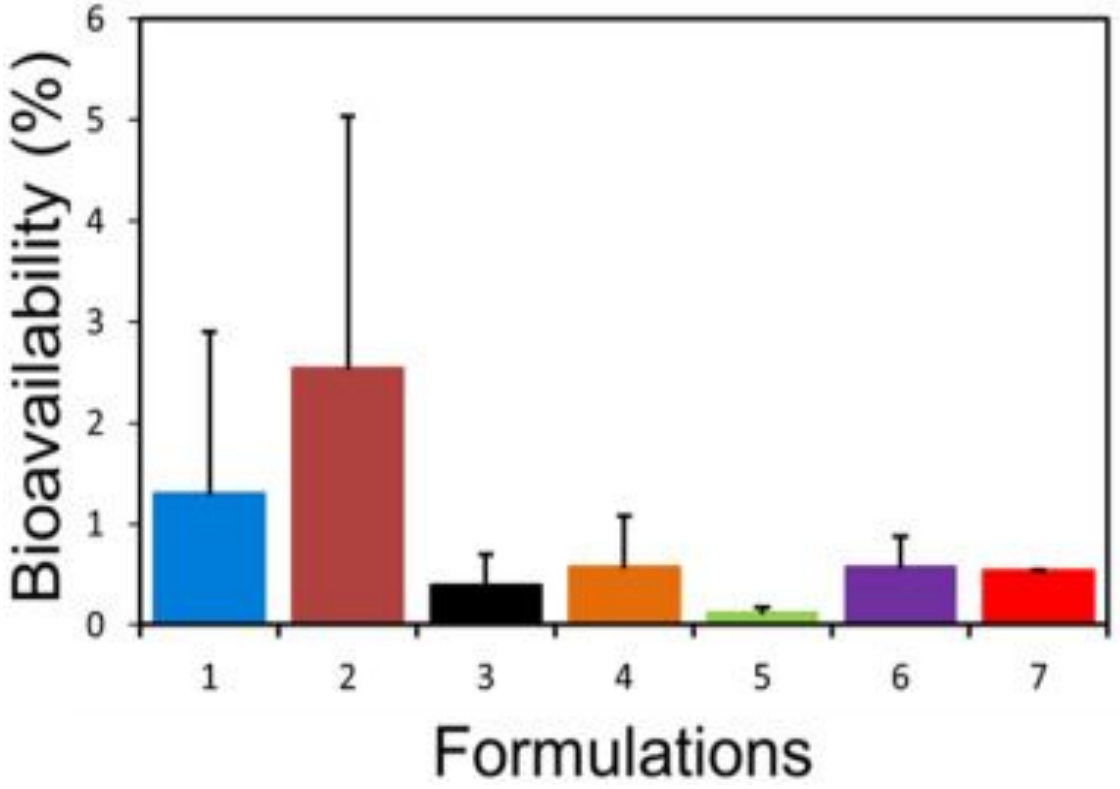
What have we learned about enhancers that we didn't know in the 1990s?

- There is a more realistic oral bioavailability target of 1-5% for peptides
- Payload selection is much more precise: potency, t½, low TI are key parameters
- Peptide stability in the GI can be assisted with inhibitors, but better still with medicinal chemistry design
- Formulation design is bespoke for the payload
- Designs need to move on from enteric-coated capsules/ tablets and matrix tablets to more sophisticated systems that can address release kinetics of payload and PE

(Maher S, et al. (2021) Expert Opin Drug Deliv. 2021;18(2):273-300)

An example of new types of oral solid dose formulations..

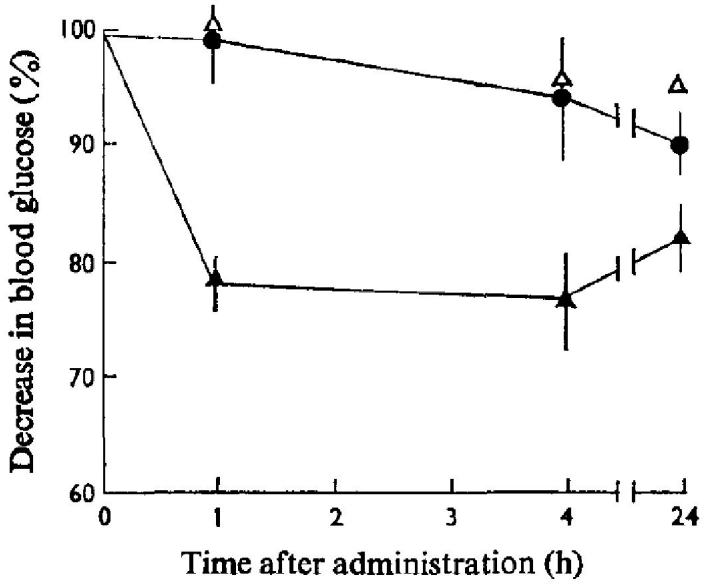




Tyagi P, et al (2021) J Control Release ;338:784-791.

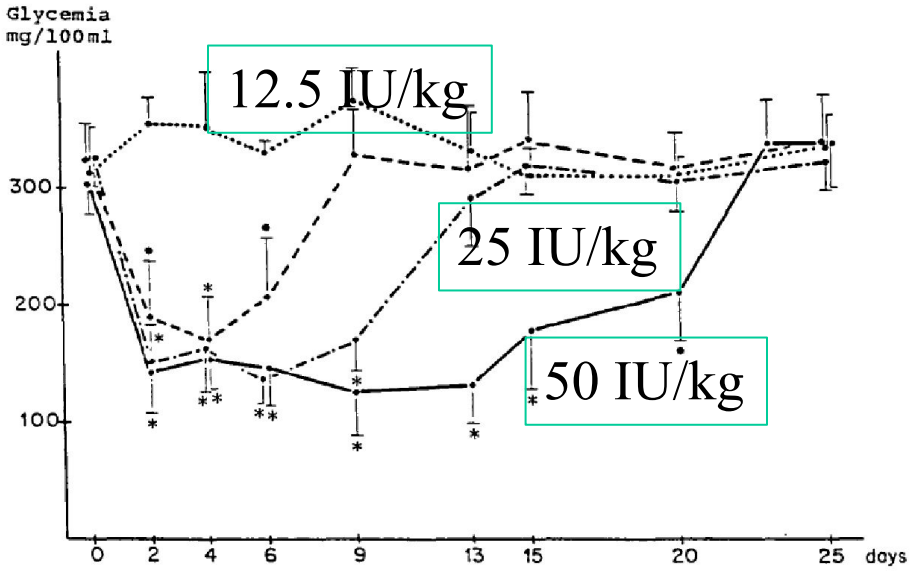
The first published data on oral insulin in nanoparticles…

Egg phosphatidyl choline liposomes in normal rats (i.g.)



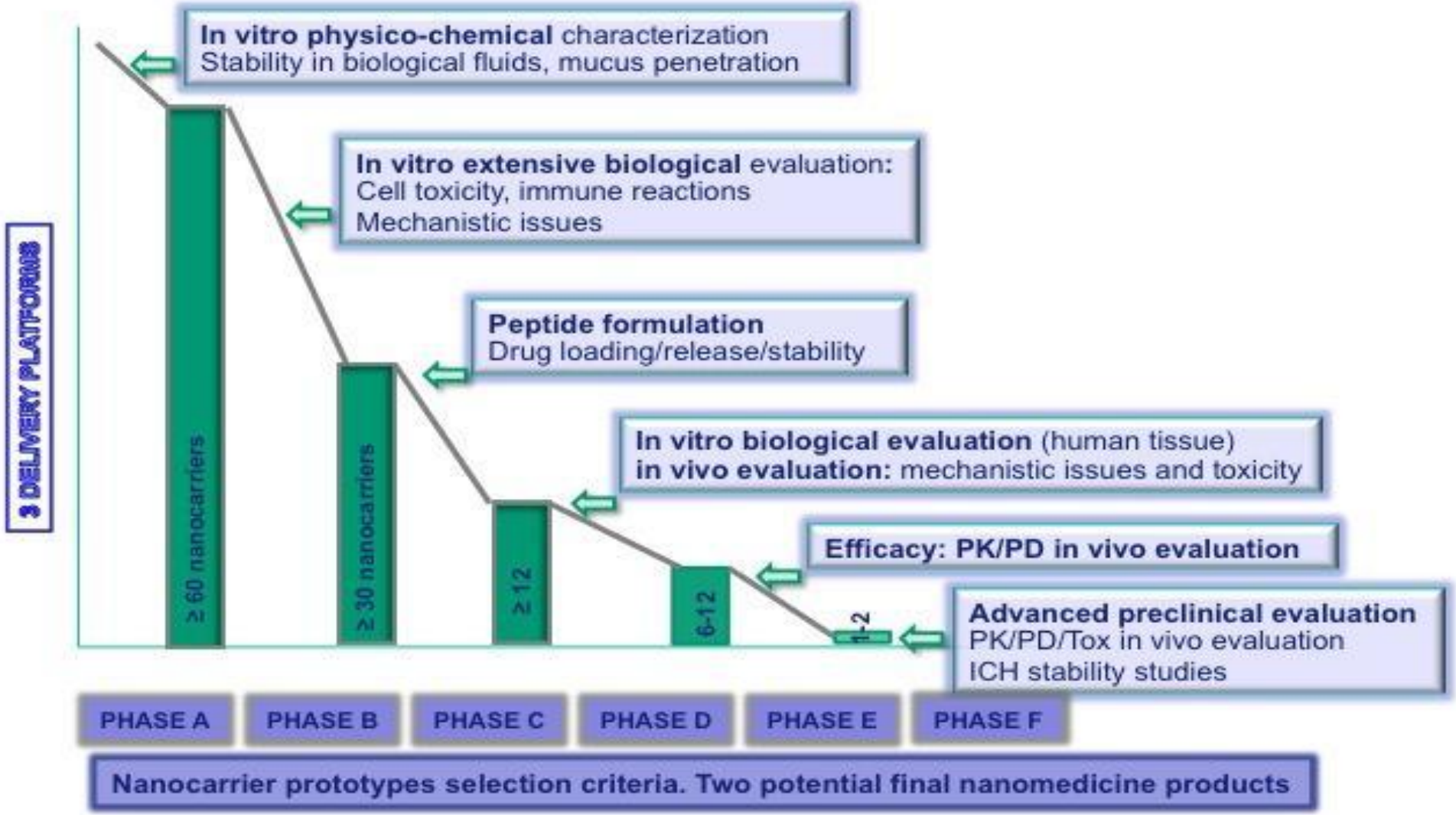
Gregoriadis, G et al (1976) Biochem. Soc. Trans. 256-259.

Polyalkylcyanoacrylate NP with poloxamer 188 and deoxycholate in diabetic rats (i.g.)

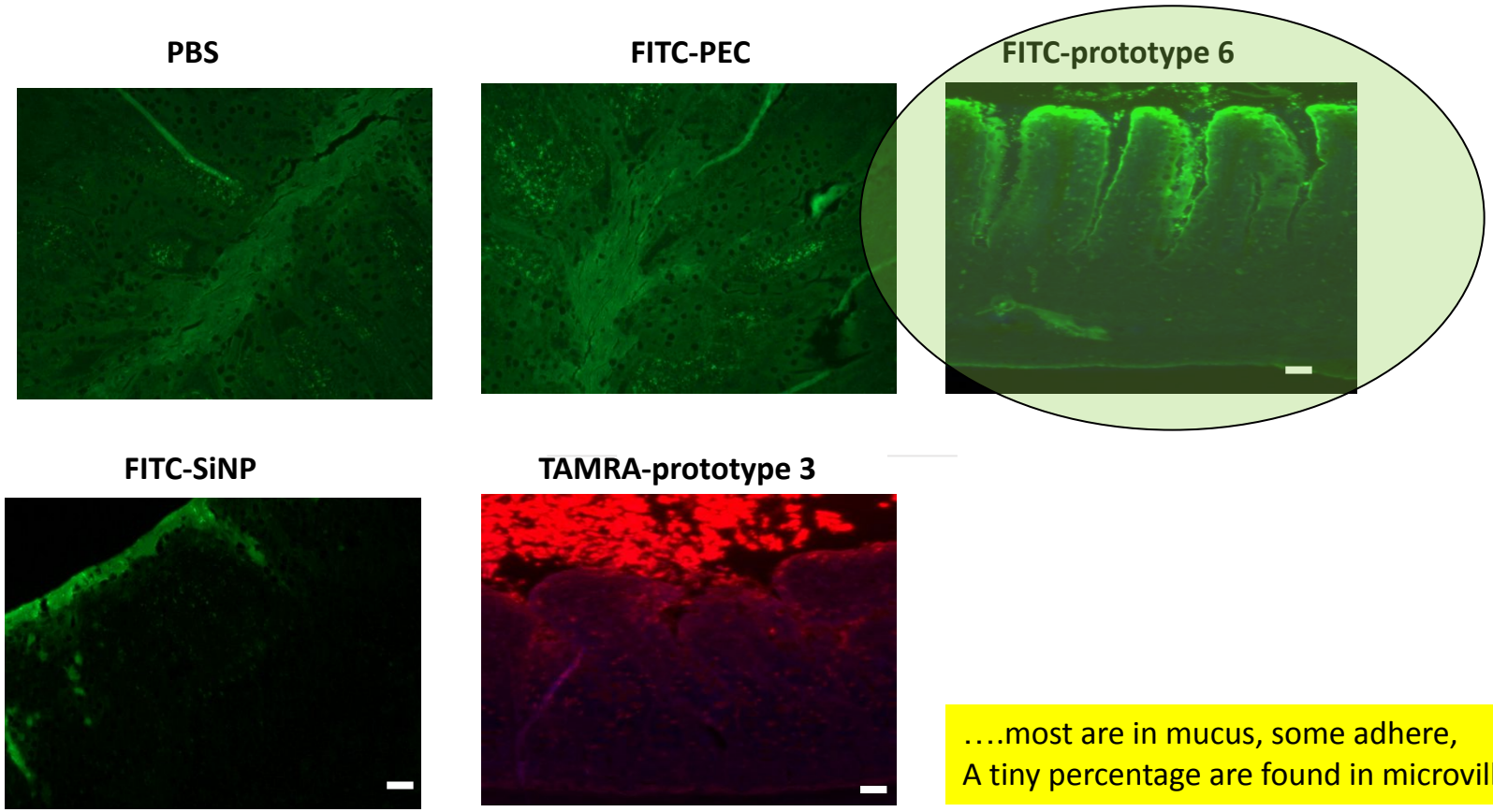


Damgé, C. et al (1988) 37:246-251.

The FP7 TRANS-INT consortium



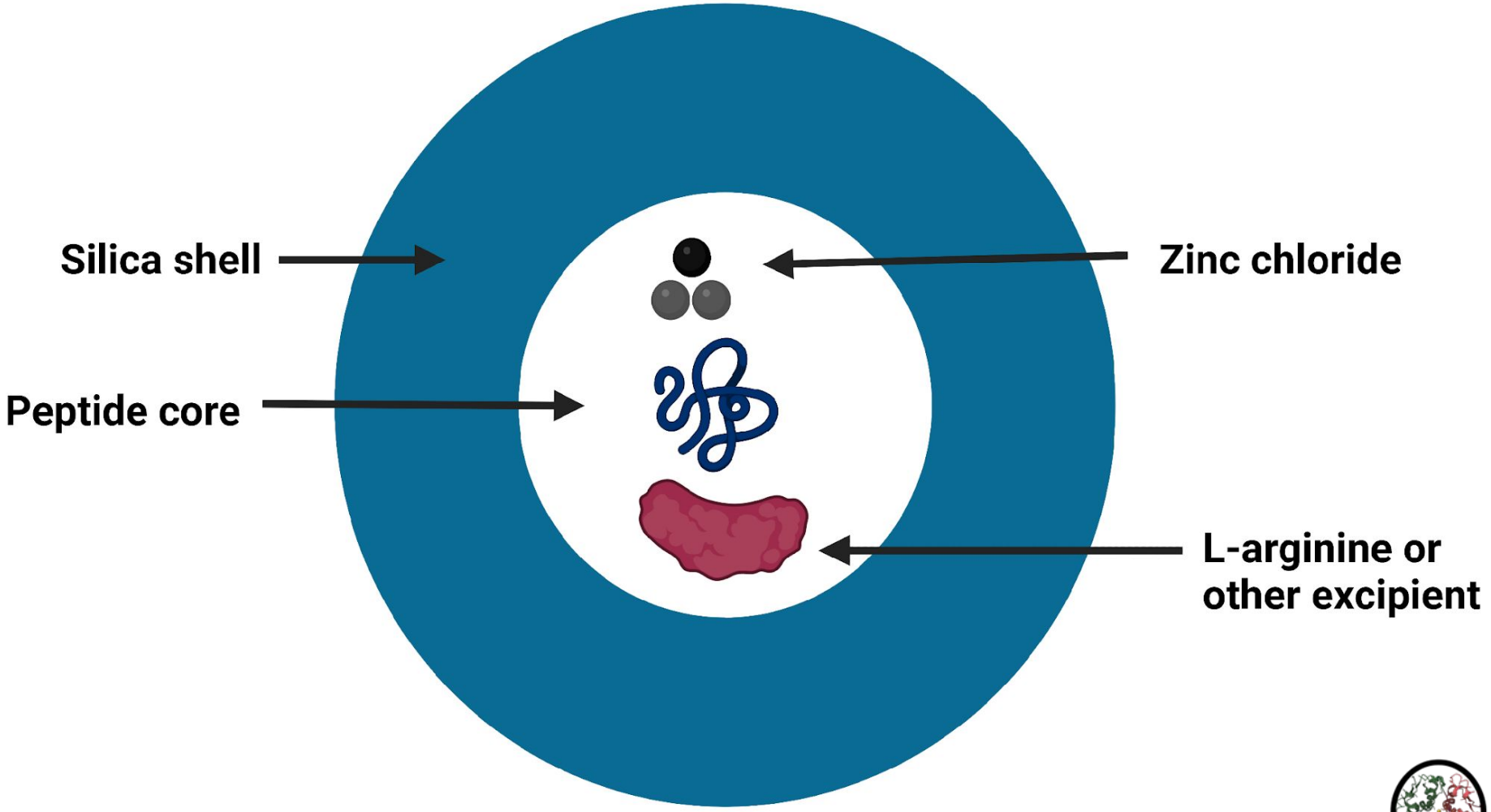
Fluorescent microscopy of jejunal-instilled nanoparticles. Ooops!



….most are in mucus, some adhere,
A tiny percentage are found in microvilli

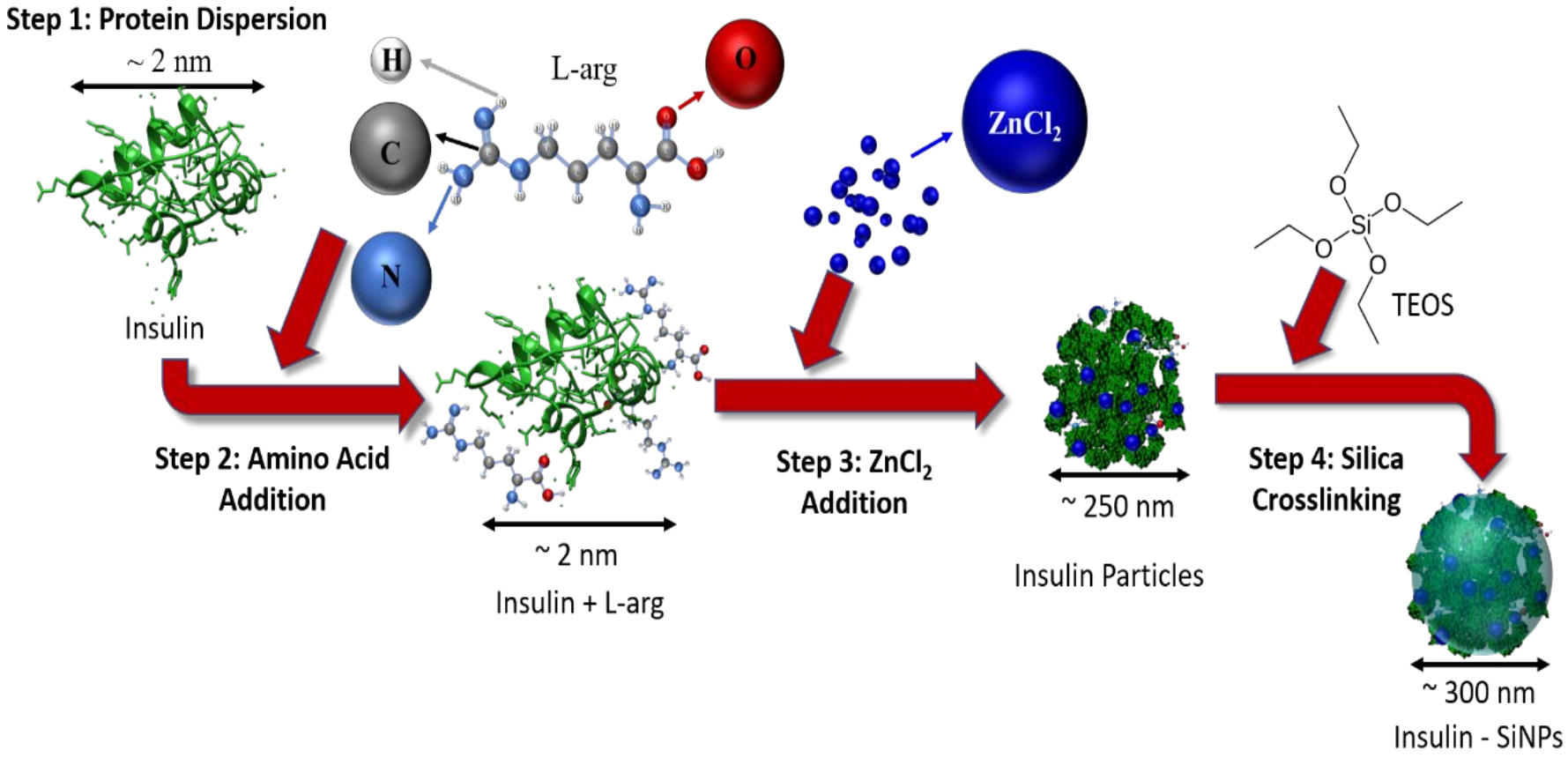
McCartney, F (2018). PhD Thesis, University College Dublin

Here's a simpler one we are working on…



Oralpep
Developing oral peptide formulations

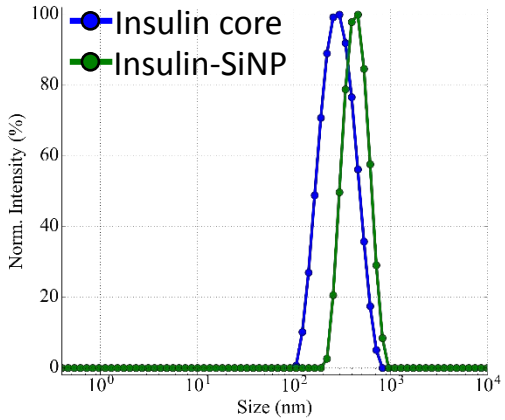
Insulin-SiNP synthesis

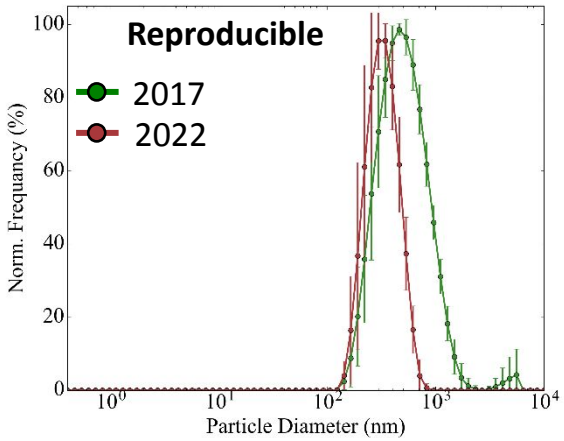


Insulin-SiNP: reproducible formulation and rat gut instillation data

Narrow size distribution

DLS size distribution



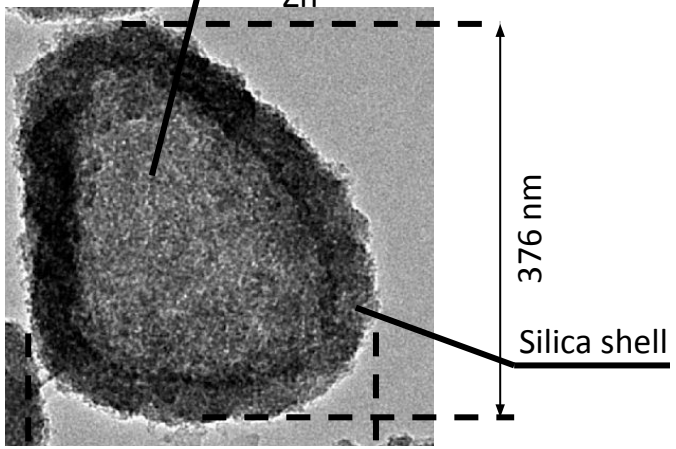


Simplicity

Four components

Peptide core

- Insulin
- Arginine
- Zn^{2+}



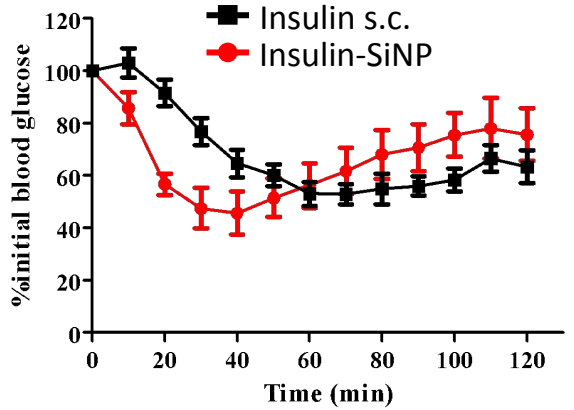
Diameters:

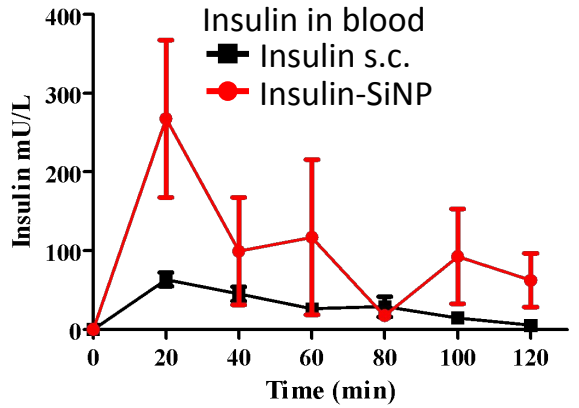
DLS ≈ 400 nm

TEM ≈ 300 nm

Functional

Blood glucose drop

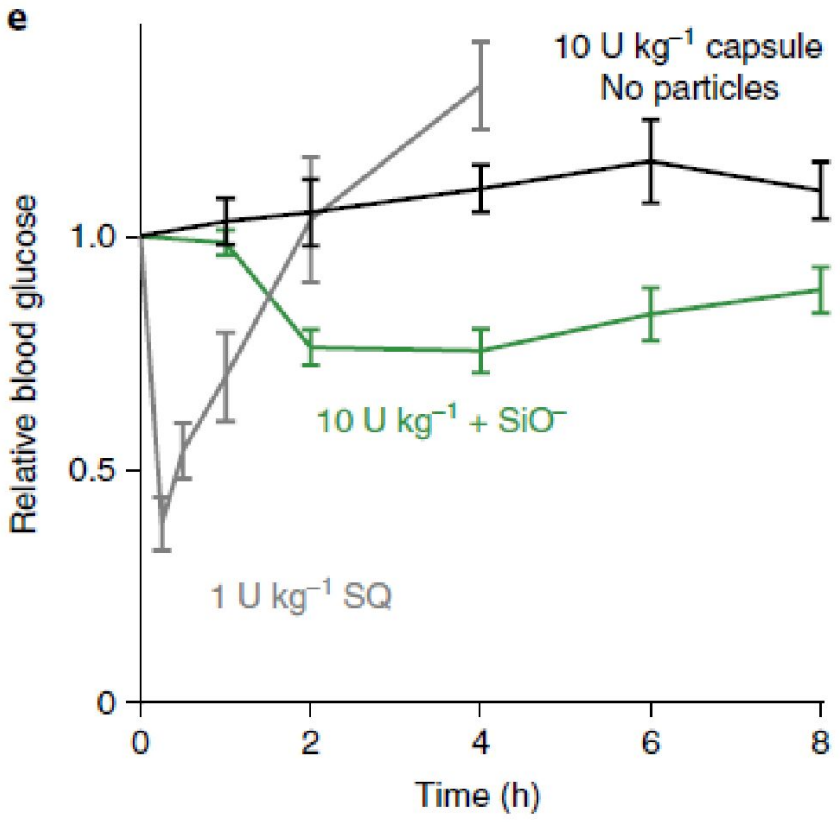


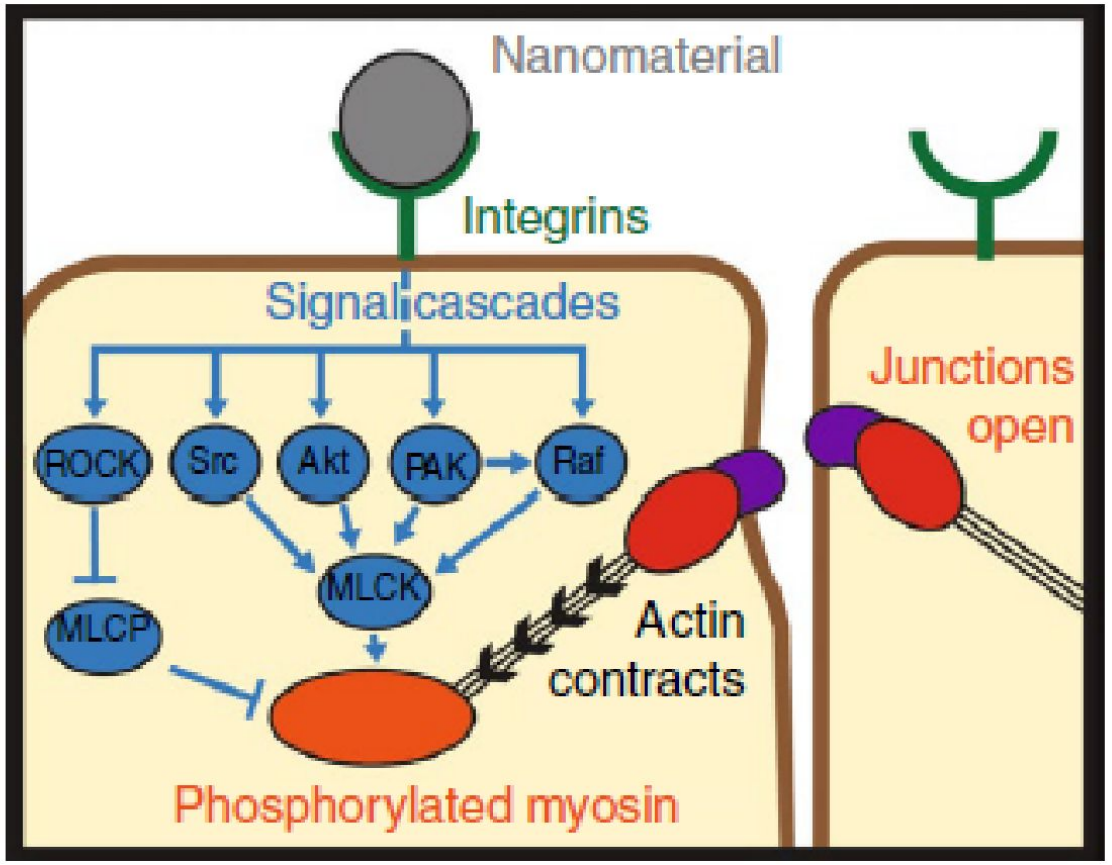


F = ~7%

A nanoparticle made from silica acting as a PE…..

Silica nanoparticles



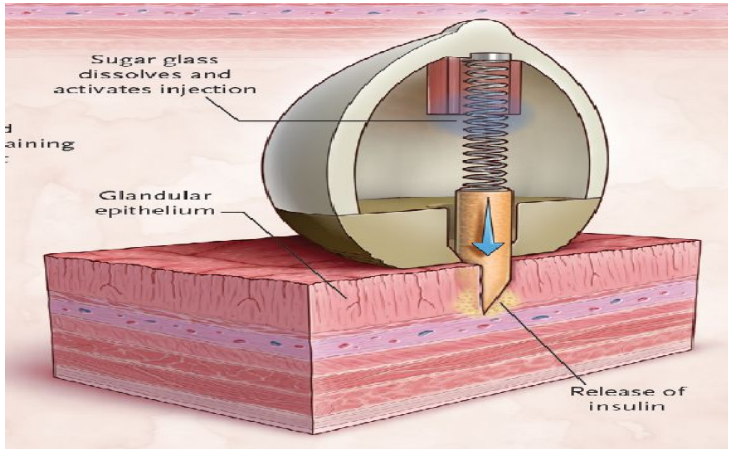


Lamson NG, et al. Nat Biomed Eng. 2020;4(1):84-96.

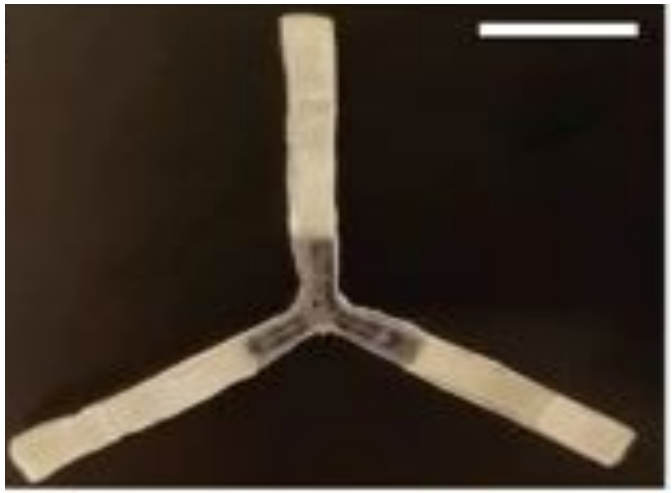
What have we learned about nanoparticles that we didn't know in the 1990s?

- The particle uptake studies carried out on Caco-2 cells bear no predictive relationship to in vivo
- We have failed to relate payload loading to the kinetics and location of release before arrival at, in, or beyond the small intestinal epithelium
- Targeted particle concepts floundered due to irreproducible synthesis, variable target expression in the GI, and over-reliance on rodent models
- The M cell route of uptake never panned out, even for oral vaccines
- We completely underestimated the physiological constraints: mucus, dilution in the GI, and rapid GI transit
- Still…there are opportunities for simple nanoparticles entrapping PEs and payloads to be developed

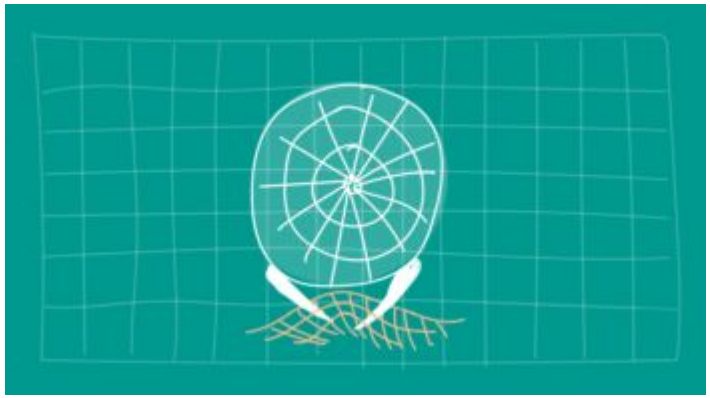
Progress in devices…



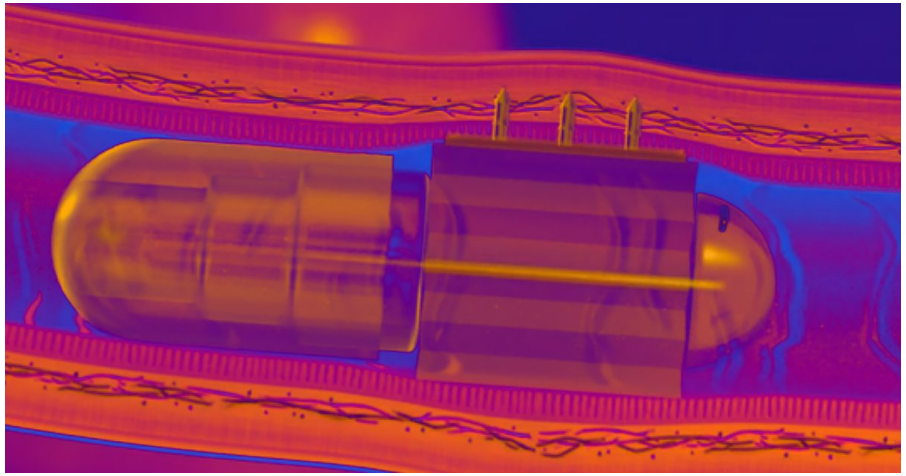
Brayden DJ, Baird AW. N Engl J Med. 2019 ;380:1671-1673.



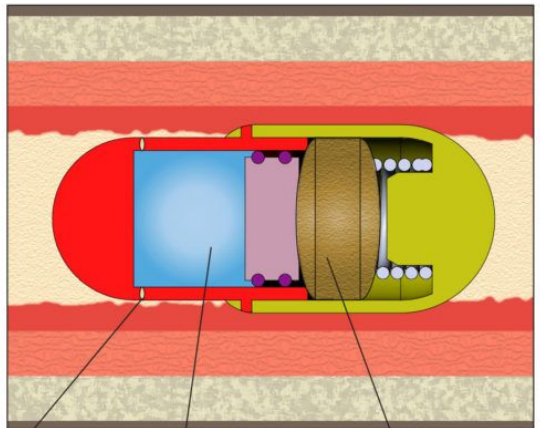
http://news.mit.edu/2019/orally-deliver-drugs-injected-1007



www.biograil.com

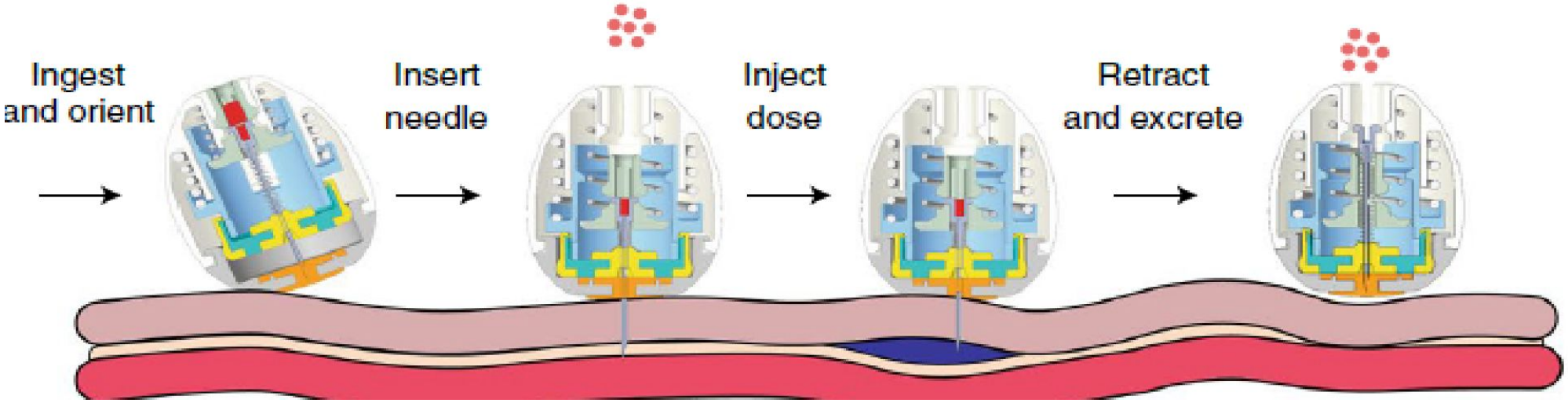


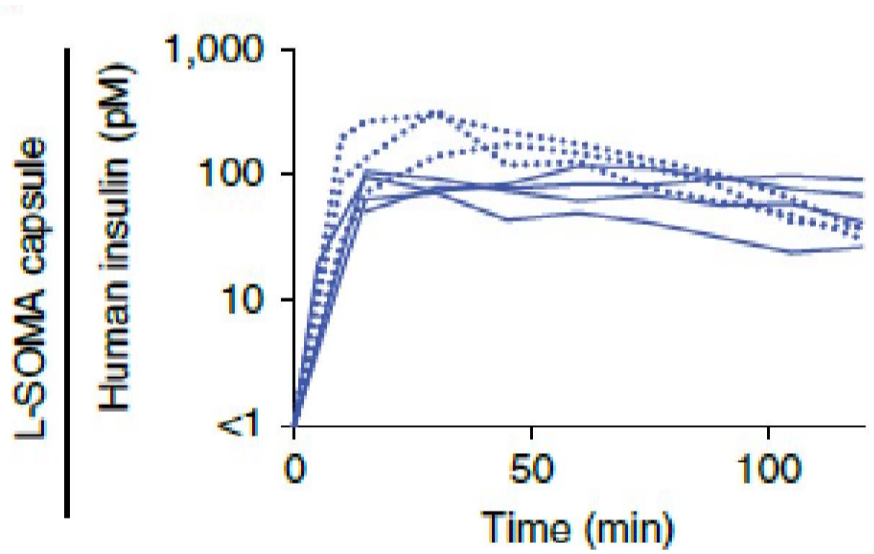
https://futurism.com/the-byte/ranipill-robot-pill-intestinal-walls

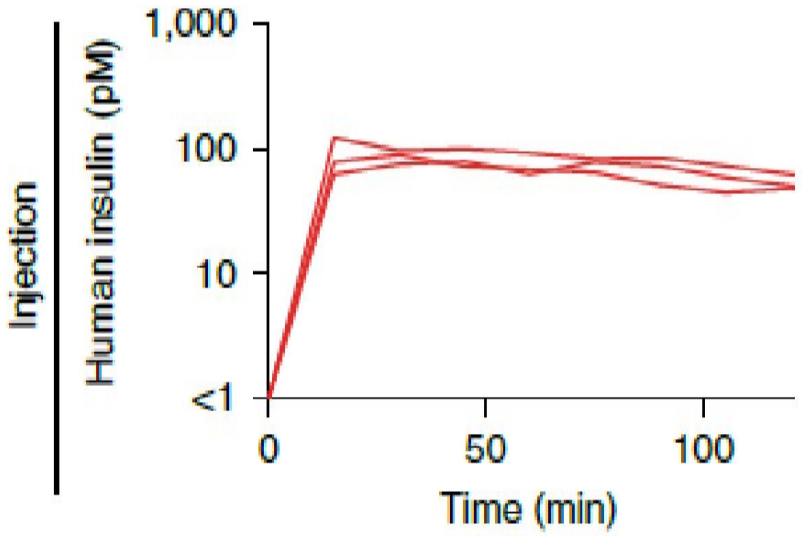


http://baywindbio.com/jetcap/#HowJetCAPWorks

L-SOMA (MIT and Novo Nordisk)

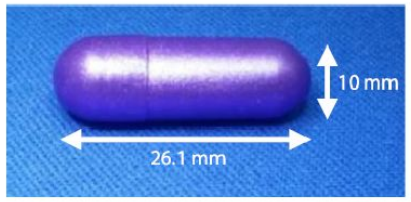


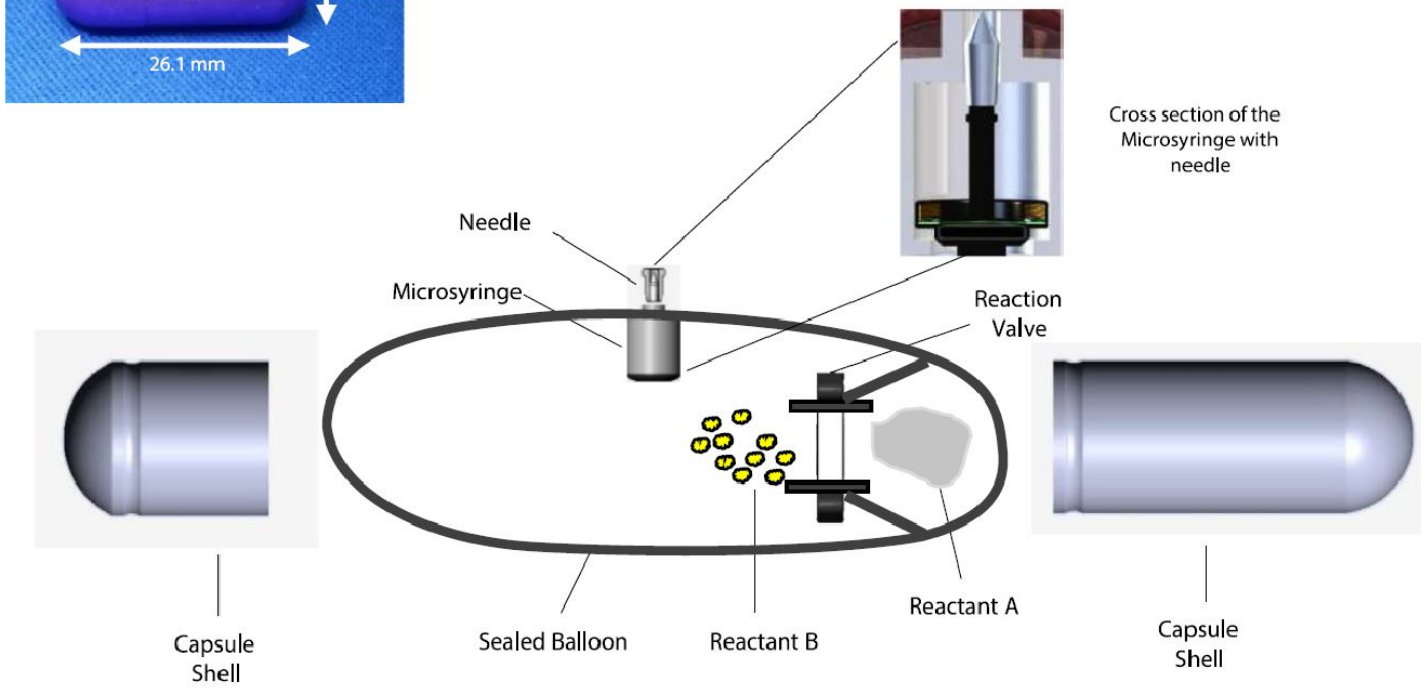


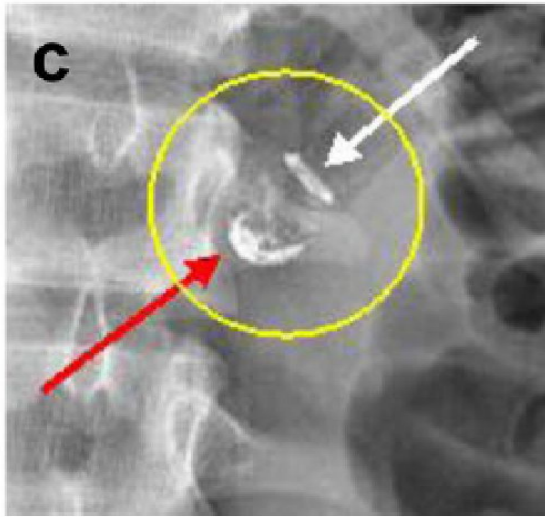


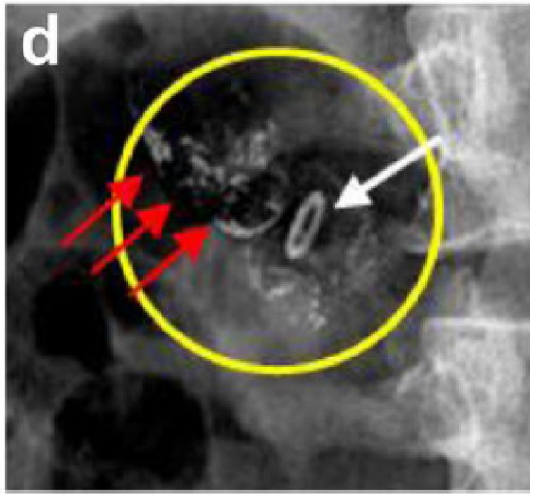
Abramson, A. et al (2021) Nat Biotechnol. 2021 Aug 30. doi: 10.1038/s41587-021-01024-0.

RaniPill™



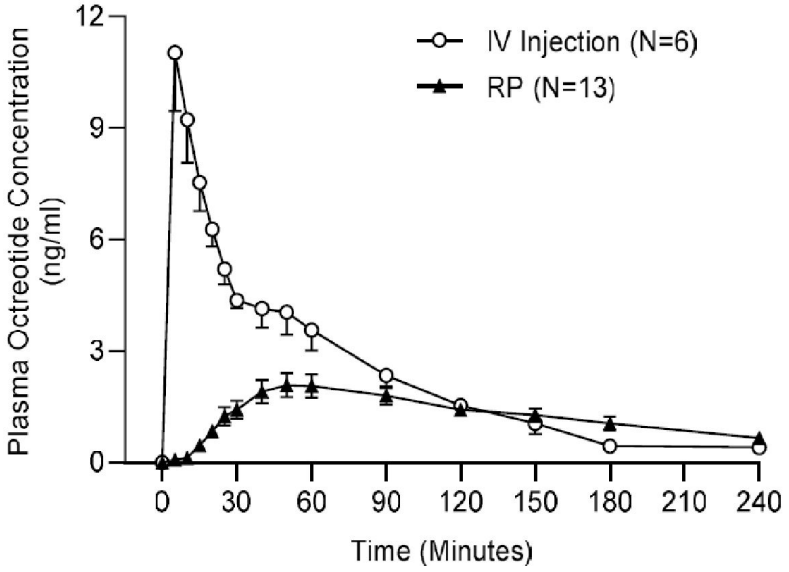


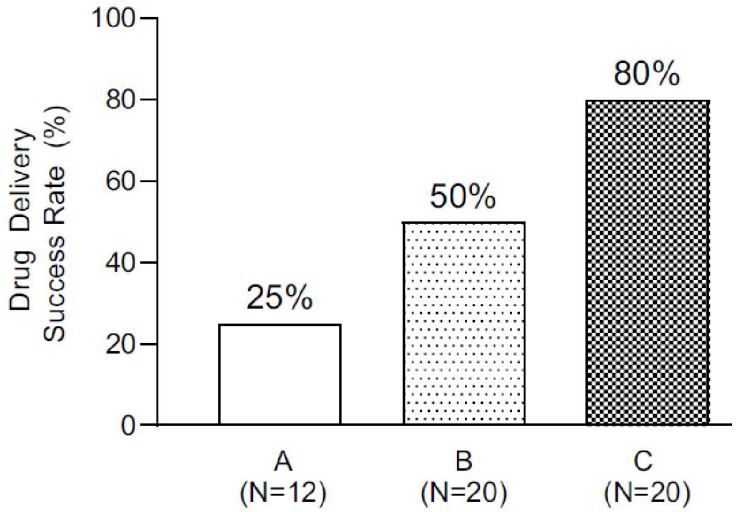




Dhalla AK, et al (2022). Drug Deliv Transl Res. 2022;12(1):294-305.

Phase I: octreotide





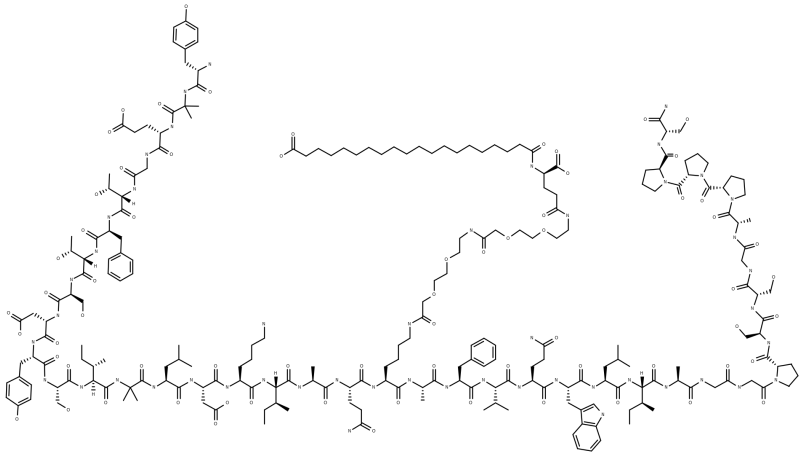
PK parameters for Octreotide administered via IV injection and RP

Group	C_{max} (ng/mL)	T_{max} (min)	$AUC_{last/Dose}$ ((min*ng/mL)/(μg/kg))	Bioavailability (% F)
IV Sandostatin (N=6)	11.1 ± 1.6	5	389 ± 22	NA
RP (N=13)	2.4 ± 0.3	50	226 ± 30	65 ± 9

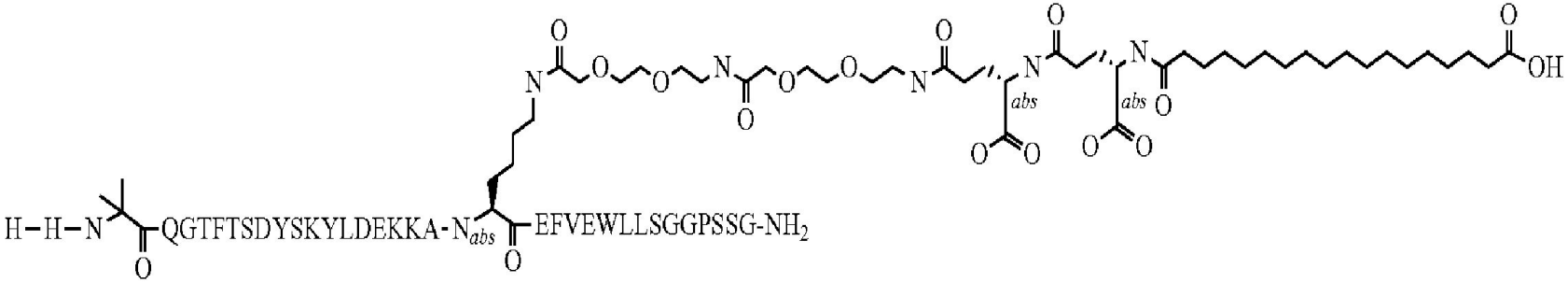
Dhalla AK, et al (2022). Drug Deliv Transl Res. 2022;12(1):294-305.

New candidates for oral: dual-acting peptides

- Once-weekly 39 amino acid GIP (glucose-dependent insulinotropic polypeptide) receptor and GLP-1 (glucagon-like peptide-1) receptor agonist (**Tirzepatide**, Mounjaro™, Lilly) given by S.C.

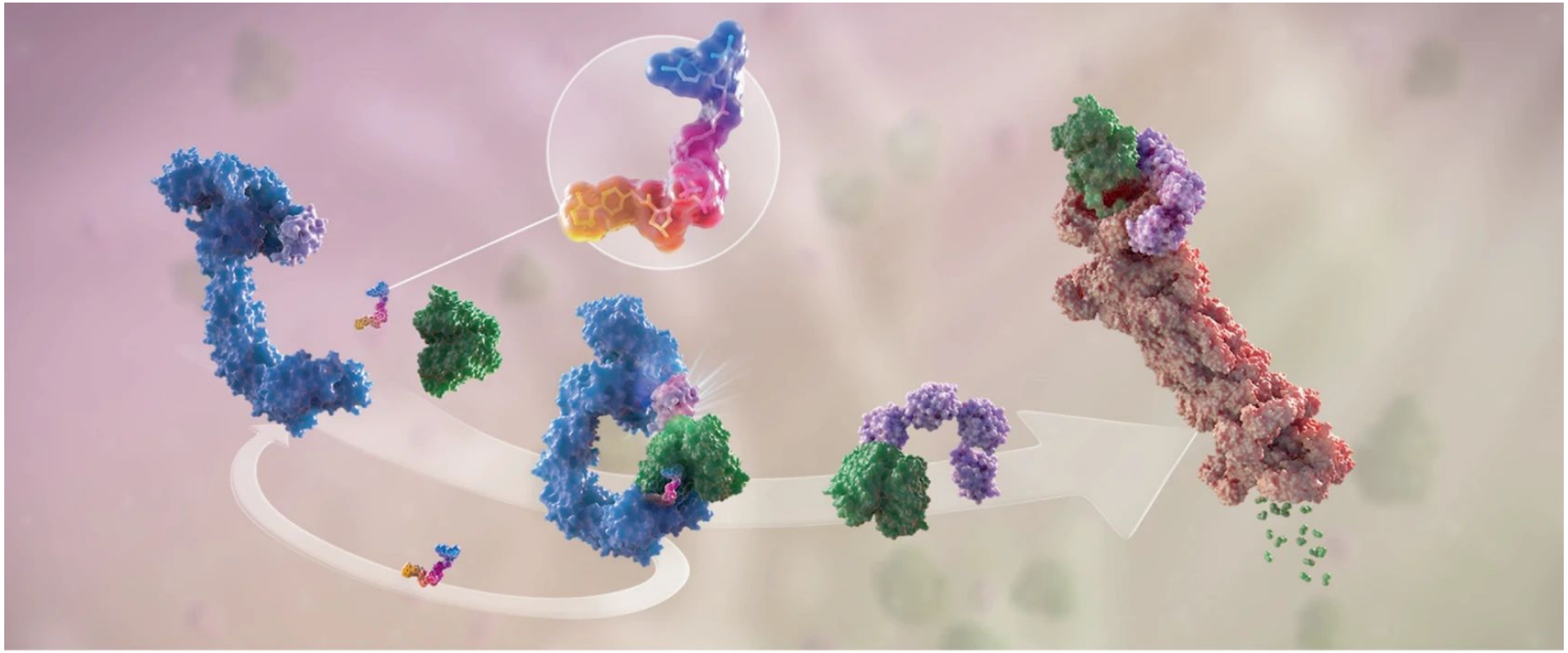


- **Acylated GLP-1-Glucagon dual agonist** (Lilly)



Mezo A. et al (2018),. USP 9,938,335 B2.

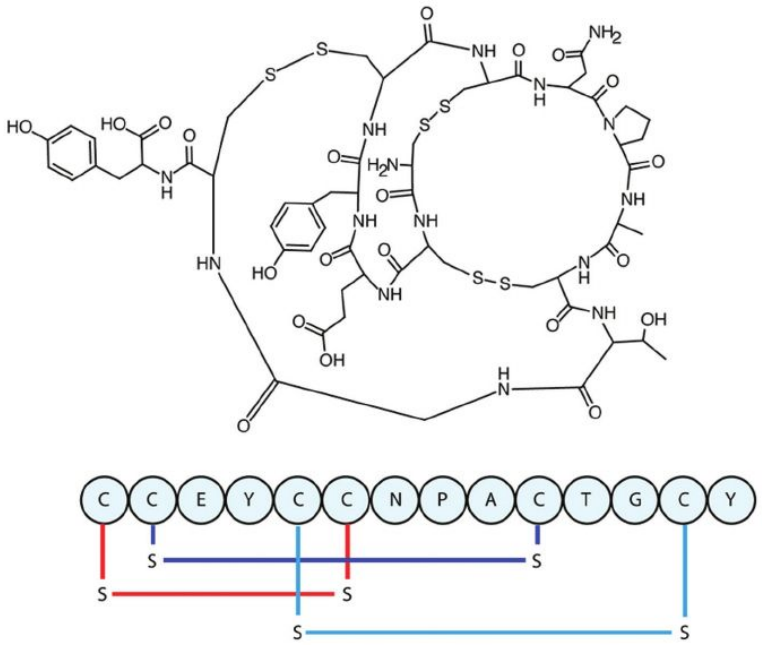
PROTACs?



Schematic the mechanism of action of proteolysis-targeted chimera (PROTAC) molecules. The PROTAC molecule (enlarged in the circle) is a heterobifunctional molecule bridging a ubiquitin ligase (in blue) and a target protein (in green). As a first step, PROTACs induce the proximity of the ligase and the substrate, such that ubiquitin (in pink) will be conjugated to the recruited substrate by the activity of the ligase. This is a catalytic step that a single PROTAC molecule can perform iteratively, enabling multiple turnover of ubiquitylation reactions, resulting in formation of ubiquitin chains on a substrate. Ubiquitin chains are then recognized by the proteasome (in red), shuttling the ubiquitylated substrate through its proteolytic chamber and degrading the target protein into small peptides (in green).

Békés M, et al (2022) Nat Rev Drug Discov. 21(3):181-200

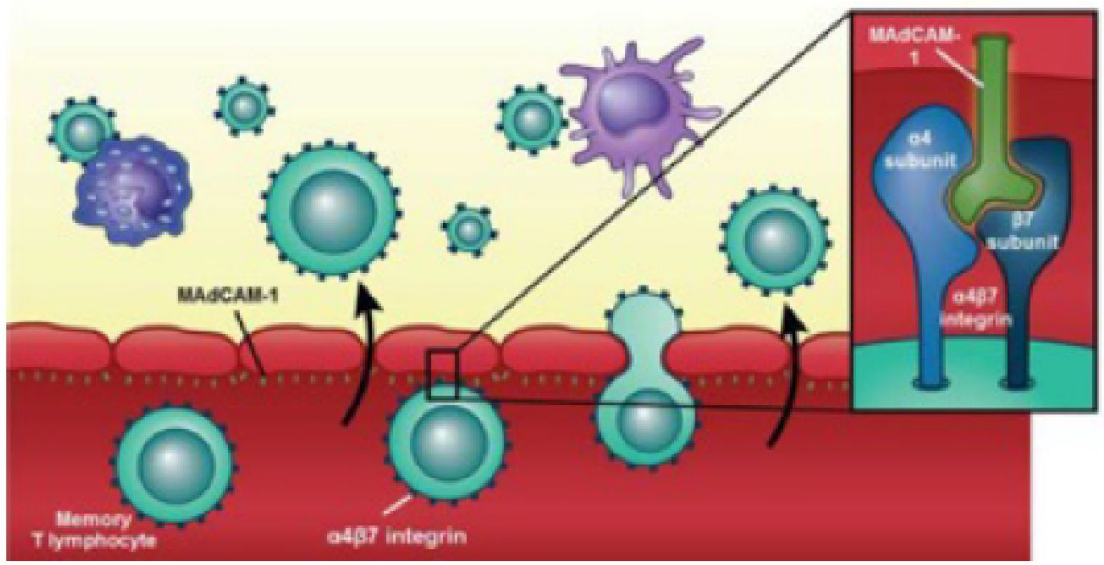
Give up and stick to local GI delivery? Gut restricted peptides



Linaclotide for IBS-C

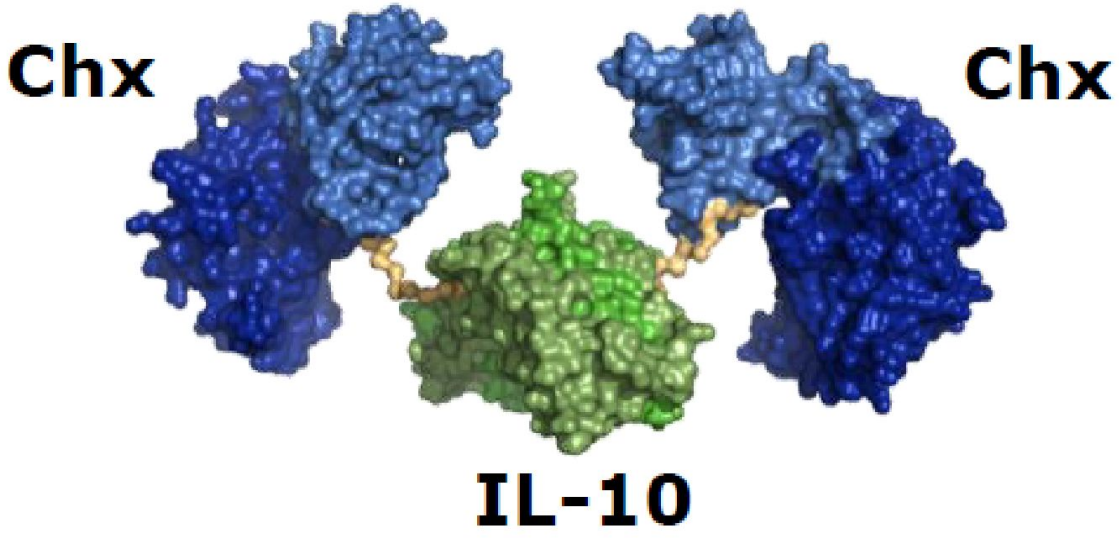
Protagonist Therapeutics

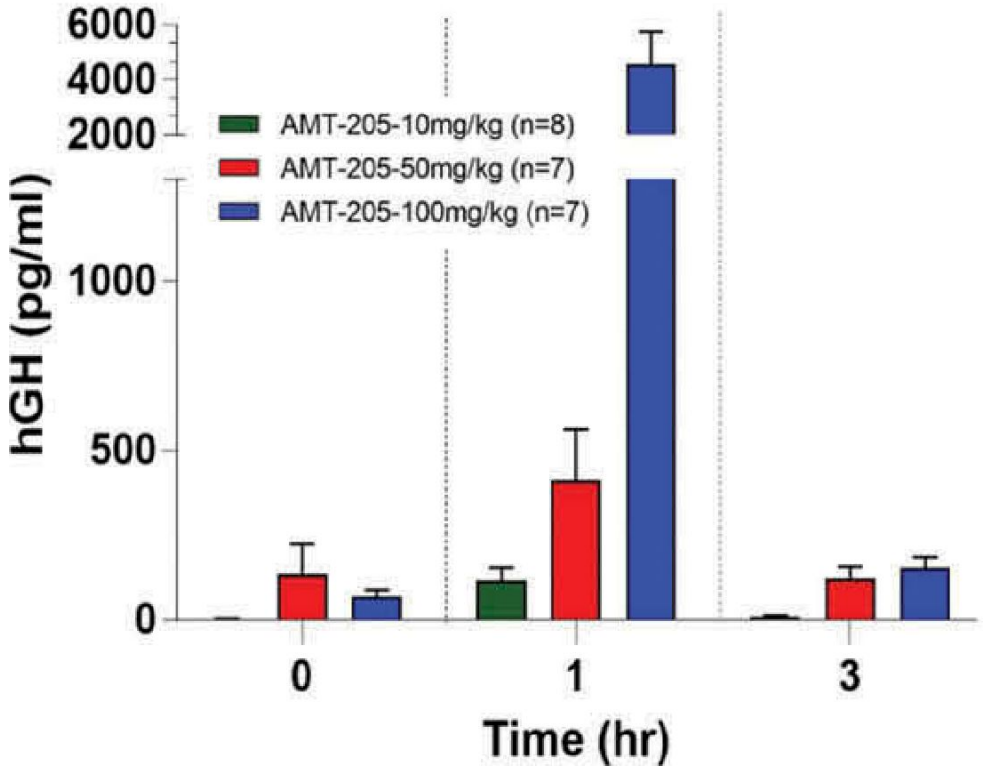
PN-943



Briskin M, et al *Am J Pathol.* 1997;151:97-110

AMT-101 IL10-fusion protein for colitis





Taverner A, et al (2020) Tissue Barriers. 8(1):1710429.

Acknowledgments and Declarations

- Declaration: DB has a current grant from Gattefosse, is on the SAB of Biograil (Denmark, and consults for Janssen (Belgium)
- The UCD Ussing and instillation studies were carried out by Dr. Fiona McCartney
- UCD's silica-based particles were made by Dr. Delyan R. Hristov
- The TRANS-INT Consortium received funding from the European Union Seventh Framework Programme (FP7 / 2007-2013) under grant agreement n°281035 (TRANS-INT)

Frontiers in Drug Delivery

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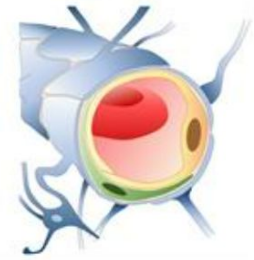
Mechanisms of Blood-brain Barrier Transport and Tight Junction Regulation

Topic Editors
Sumio Ohtsuki, Siti R Yusof, Ignacio Romero, Shinya Dohgu and Patrick T. Ronaldson



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