Biological Strategies for the Oral Delivery of Poorly Absorbed Therapeutics

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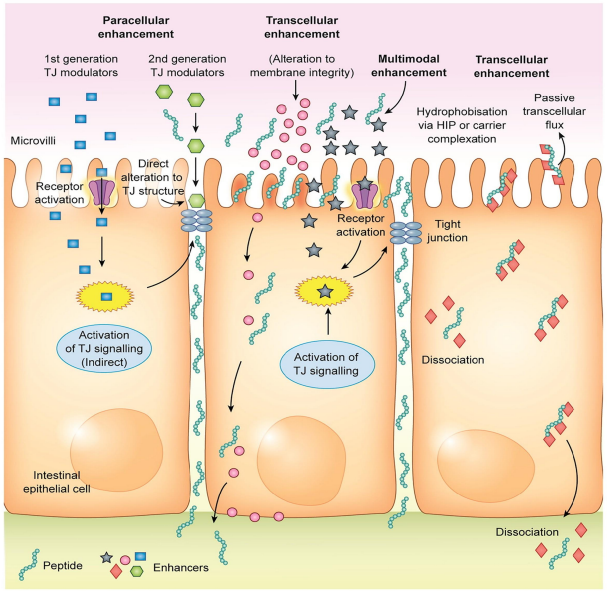
NEXT-GENERATION DELIVERY INNOVATIONS

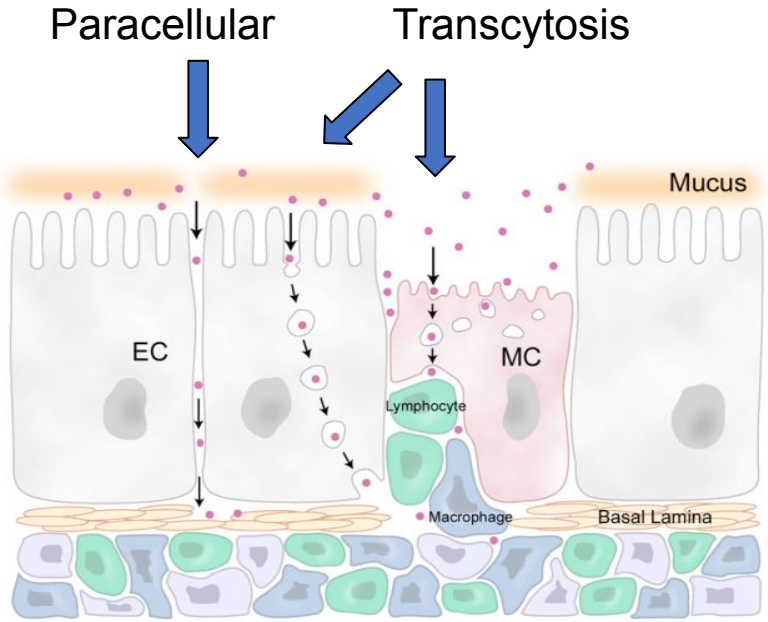
Paracellular vs Transcellular Transport



Zhu, et al., 2021 *Acta Pharm Sinica B.*, 11:2416

- Intestinal barrier is constantly confronted with massive loads of materials through our diet and resident the intestinal microbiome.
- That barrier is highly efficient at selectively sorting these materials for uptake versus exclusion.
- Particles (think viruses) and non-self intact proteins and peptides are excluded to limit infection outcomes and to maintain homeostasis.

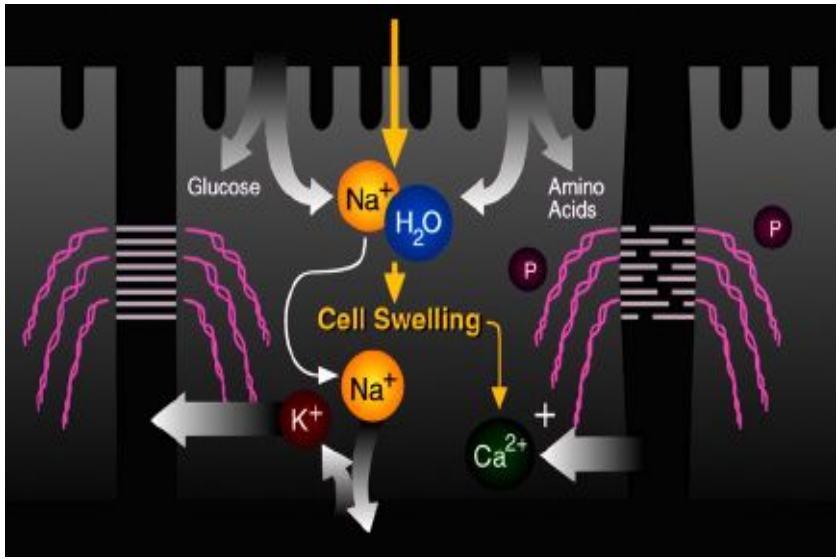
Endogenous Pathways

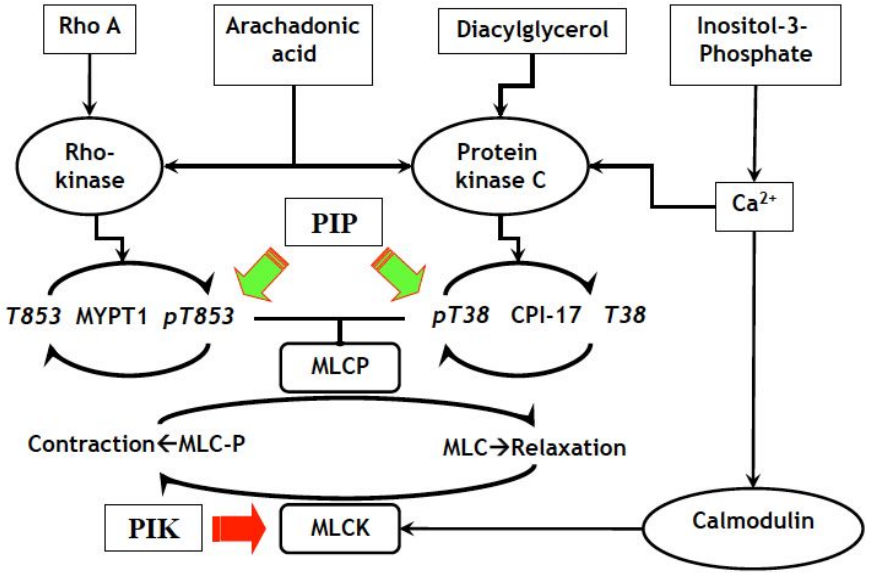


Jung, et al. 2000 *Eur. J. Pharm. Biopharm.*, 50:147-160

- The intestinal epithelium is a dynamic barrier constantly under repair and being replaced every 3-5 days.
- There are apical surface transporters to specifically take up amino acids, nucleic acids, sugars, vitamins (co-factors), etc.
- Two major systems are in place to manage selected uptake of materials without a surface transporter.

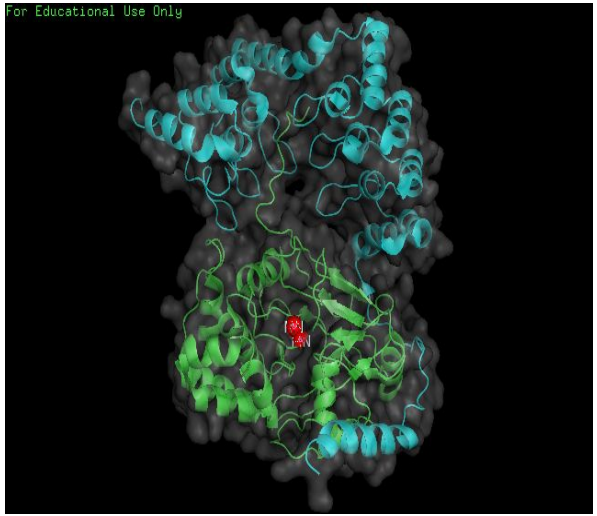
Nutrient-Driven Paracellular Transport



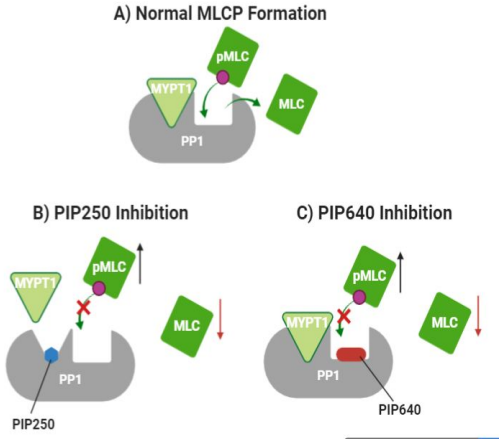


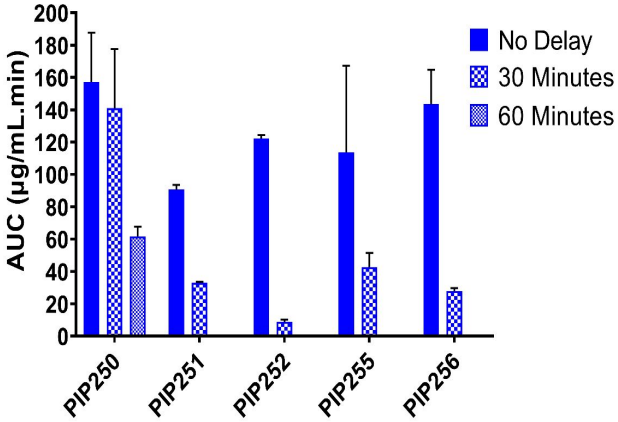
Daugherty and Mrsny, 1999, *Pharm. Sci. Technol.* 2:281-287

MYPT1-PP1 Protein Interactions



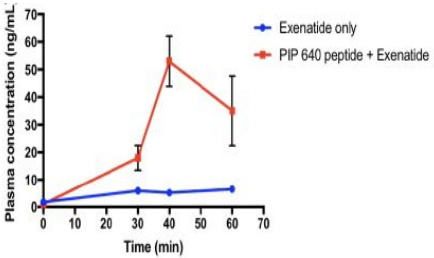
Terrak *et al* 2004 *Nature 429:780*

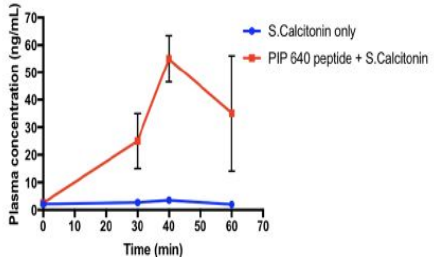


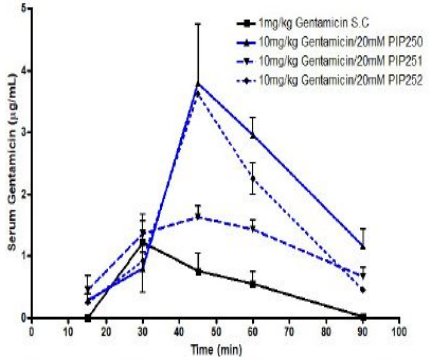


Almansour *et al* 2018 *J Controlled Rel* 279: 208
Taverner *et al* 2023 *J Controlled Rel* 364:357

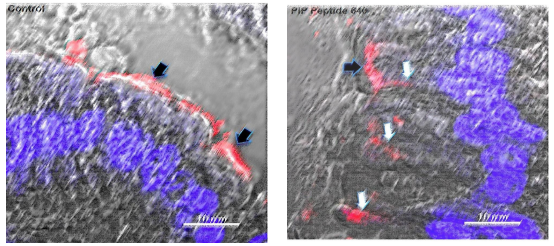
In Vivo Delivery of Clinical Candidates

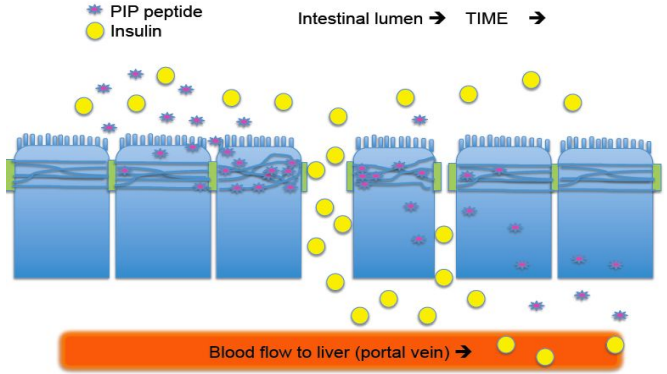






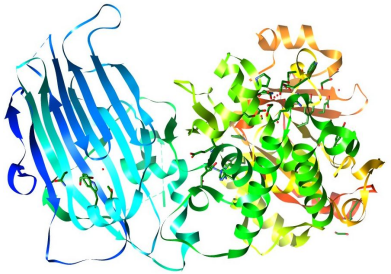
Peptide	T_{max} (min)	C_{max} (µg/mL)	AUC (µg/mL·min)	F_{REL}
PIP250	45	3.79 ± 1.67	155 ± 30.4	36.5%
PIP251	45	1.63 ± 0.31	90.5 ± 2.9	21.3%
PIP252	45	3.62 ± 0.02	127.4 ± 2.1	31.0%



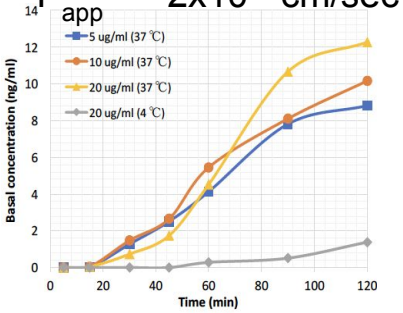


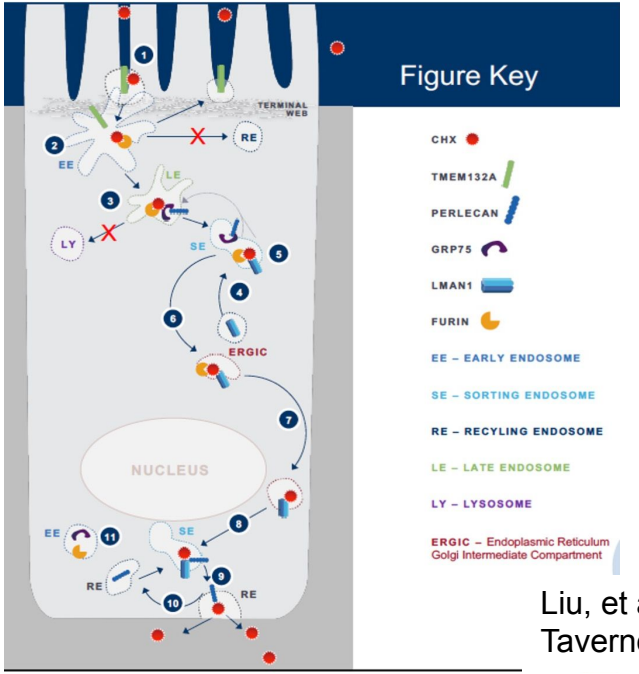
Almansour *et al* 2018 *J Controlled Rel* 279: 208
Taverner *et al* 2023 *J Controlled Rel* 364:357

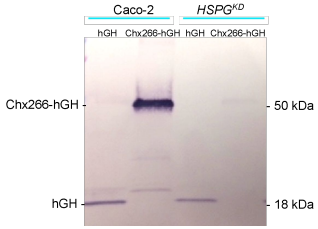
Cholix (Chx) uses Active Transcytosis to Enter

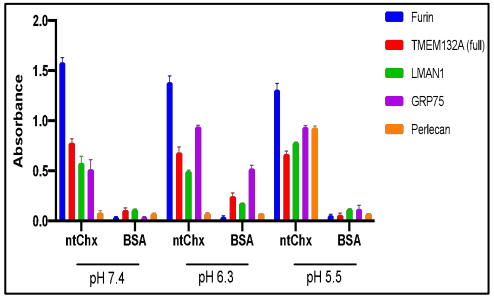


P_{app} = ~2x10^{-5} cm/sec



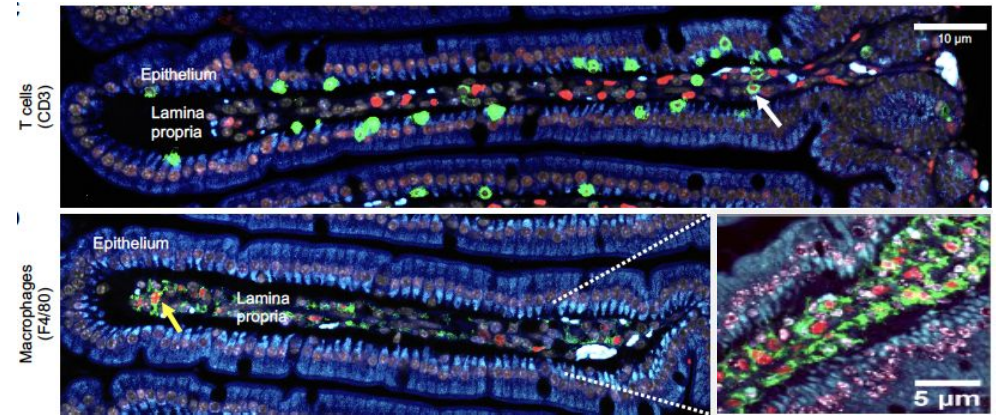


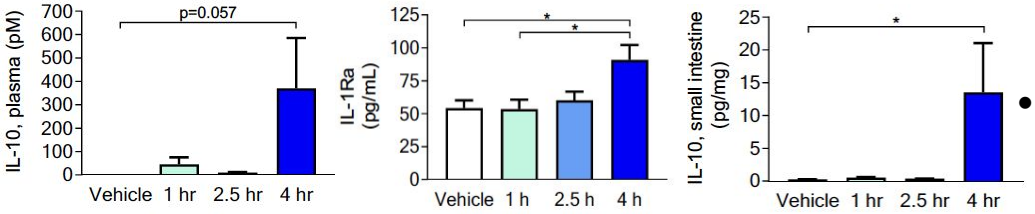




Liu, et al., 2022 *Tissue Barriers,* 11(1):2039003*;*
Taverner, et al. 2020 *Tissue Barriers, 8(1):1710429.*

Preclinical Validation of AMT-101

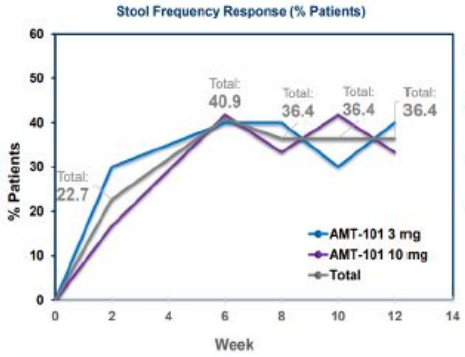




- Interleukin-10 (IL-10) is a potent anti-inflammatory cytokine
- Systemic administration of IL-10 causes serious anemias.
- Chx genetically conjoined to hIL-10 = AMT101.
- AMT101 delivers biologically active IL-10 to lamina propria cells after intestinal dosing.
- IL-10 delivered by AMT101 stays in the intestinal mucosa.

Fay et al. 2020 *J Immunol, 205(11):3191-3204.*

Phase 2 Readout of AMT-101 in Pouchitis

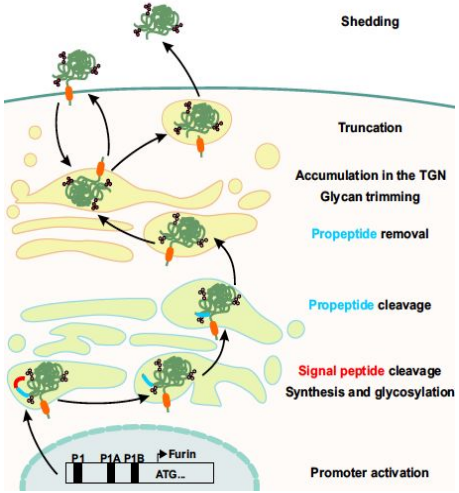


- AMT-101 demonstrated a rapid onset of stool frequency response as early as week 2
- Rapid response is consistent with Phase 1b data in UC patients
- Clinical response was maintained through duration of treatment in both dose arms
- Top-line interim data demonstrated additional symptomatic improvements in fecal urgency, incontinence and abdominal cramps

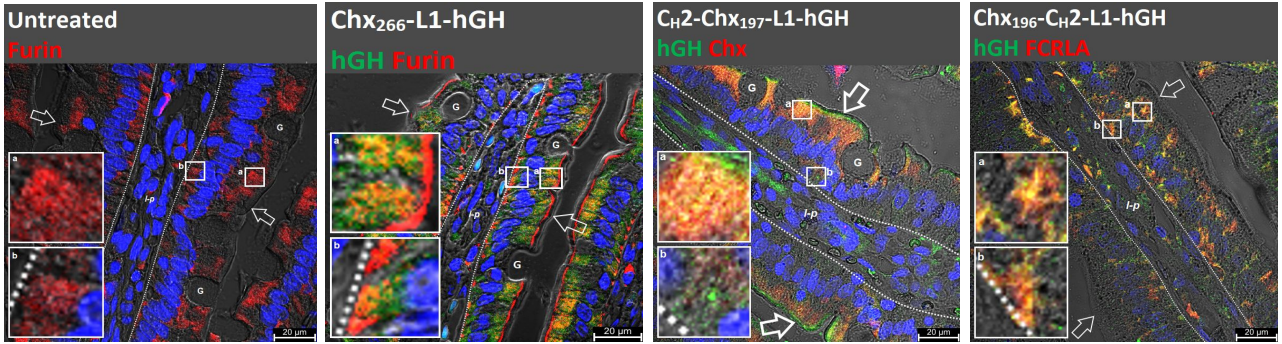
Pre-specified Efficacy Endpoint	Endpoint Definition	Patients Achieving Response, n(%) AMT-101 3mg (n=10)	AMT-101 10mg (n=12)	Total (n=22)
Stool Frequency Response (%) at Week 12	Reduction of = 3 stools and = 30% from baseline, OR = post-colectomy normal	4 (40.0%)	4 (33.3%)	8 (36.4%)
Histologic Healing Response (%) at Week 12	Geboes score = 3.1	2 (20.0%)	3 (25.0%)	5 (22.7%)

- Chx proven safe in multiple Phase II studies (hundreds of exposures).
- Promising outcome for pouchitis patients but not for colitis patients.
- Data demonstrates successful oral delivery using an enteric-coated solid dosage form to small intestine.
- Interleukin-10 (IL-10) is a potent anti-inflammatory cytokine
- Proves pathway in human intestine for repeat dosing for a biologically active biopharmaceutical.

Systemic Delivery is Complicated

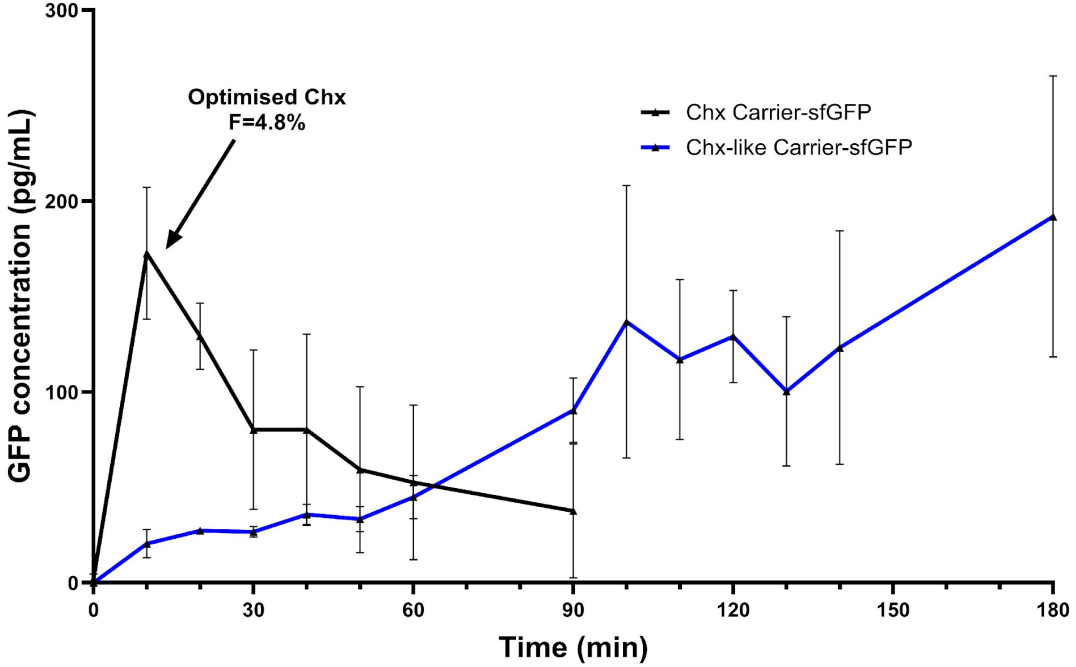


Braun & Sauter 2019 *Clin Transl Immunol* e1073; Taverner *et al* 2025 *J Controlled Rel* Jun 17:113964



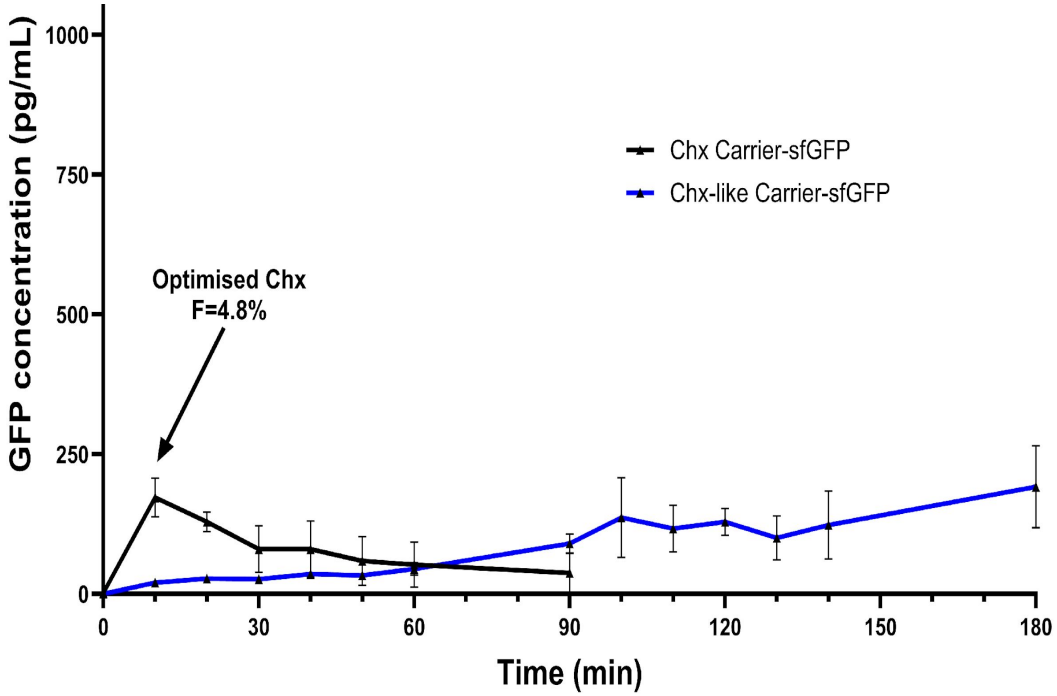
- Chx induces furin to move to the apical surface
- Inclusion of human IgG1 element C_H2 results in a greater amounts of intact chimera getting to the apical vesicular compartment and systemic cargo delivery.
- Inclusion of C_H2 results in colocalization with FCRLA and deviation from furin scission in the apical region.

Impact of C_H2 on Chx Oral Delivery



- C_H2-Chx-hGH results in ~5 % bioavailability (F) in systemic circulation in rats.
- C_H2-Chx-like carrier produced a slower onset of serum levels yet overall greater overall F than C_H2-Chx.

A Different View



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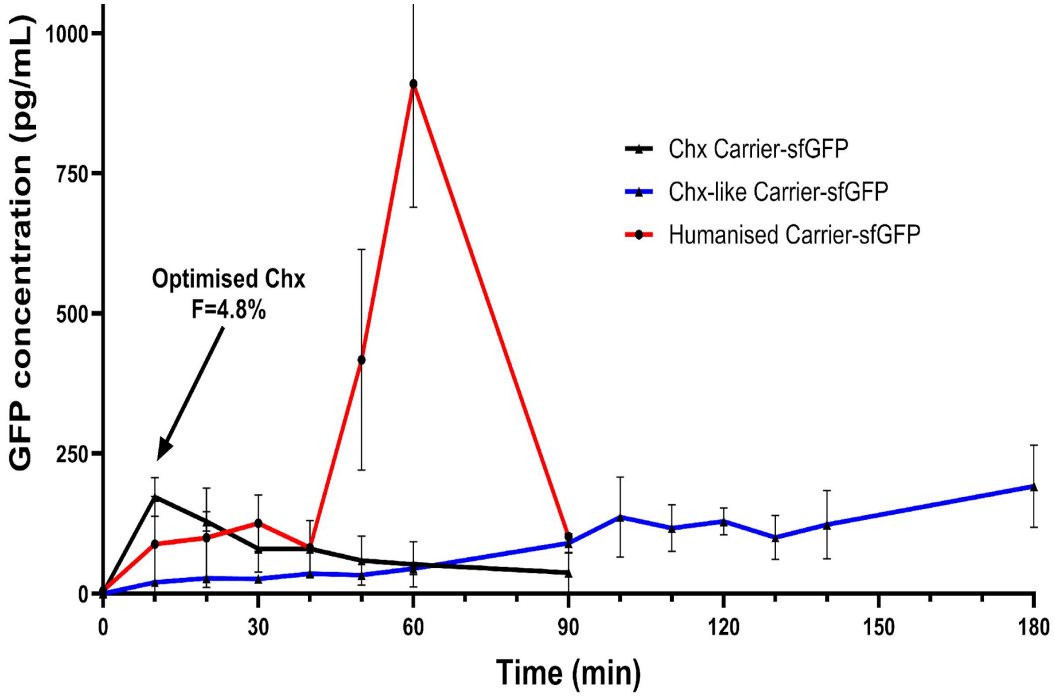
A “Humanised” Carrier Looks Very Promising



- We identified a human protein that can be modified with only 10 amino acids to produce a striking systemic F.
- This “humanized” carrier should provide a platform for oral biopharmaceutical delivery.

Those Who Made it Happen

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Anna Weiss, John Waters
Maziyar Saberi, Apurva Chandalia
Nicole Fay, Nayaki Muthusamy
Sabrina Lei, Jessie Jia
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