Global Drug Delivery and Formulation Summit 2025

Challenges in Oral Peptide Delivery and ways of to overcome them

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CRS 2025 ANNUAL MEETING & EXPOSITION
PHILADELPHIA, PA
JULY 13-18, 2025
NEXT-GENERATION DELIVERY INNOVATIONS

Challenge in Oral Peptide Delivery

- Unable to pass the mucus layer and GI epithelium resulting in poor bioavailability.
- Still limited understanding how to get across GI barriers due to their complexity.
- Systematic empirical testing of different drug delivery approaches required but lack of suitable model system that capture GI complexity while allowing HTP screening.

GI-ORIS™ Workflow

Enables Screening of Thousands of Samples per Day with excellent *in vivo* Predictability

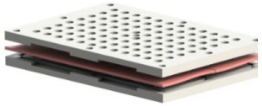
Formulations

~ 12,000 unique formulations

Ex vivo GI Tissue Methods

Fully Intact & functional GI Tissue Explants

Interface Device

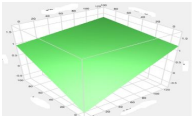


GI Tissue in Microplate Format

Screening

HTP GIT Absorption Screening

Data



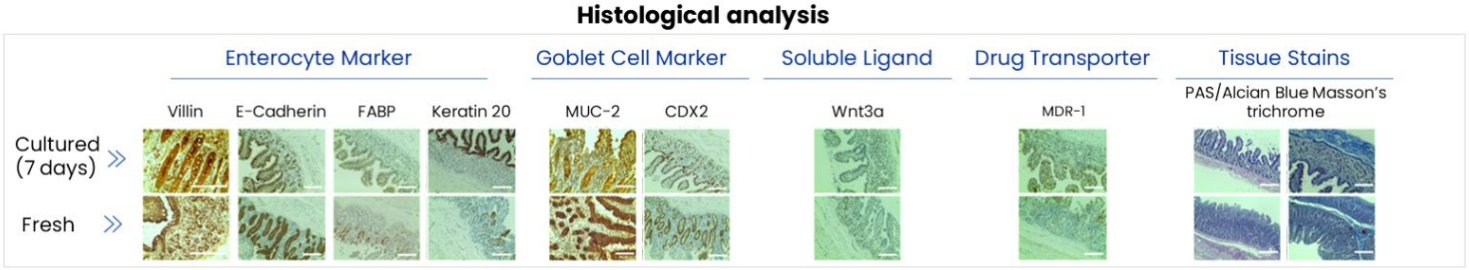
All screening data stored in growing database

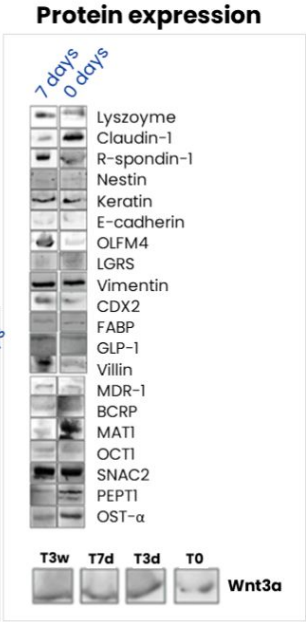
- Intact tissue in 6-384 Well Plate Format
- Tissue can be removed for further analysis
- Can use any tissue from esophagus to rectum
- Compatible for solid dosage formulations

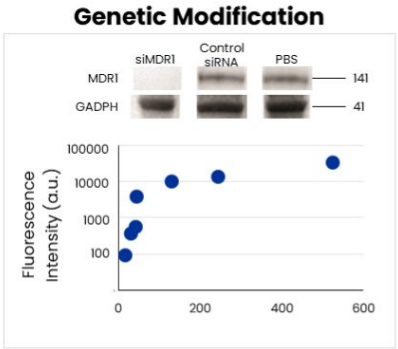
- Oral Bioavailability Enhancement
- Local GI tissue API/Biomarker or efficacy evaluation
- GI segment evaluation
- Native fluid/food absorption evaluation
- GI toxicity evaluation

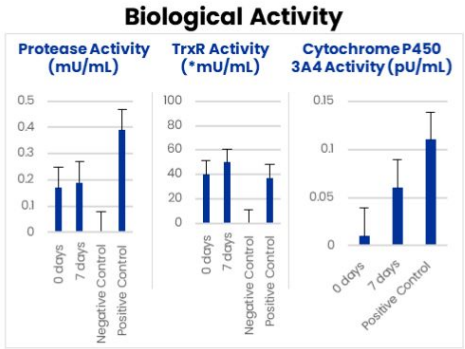
GI-ORIS™ GI Tissue Characterization

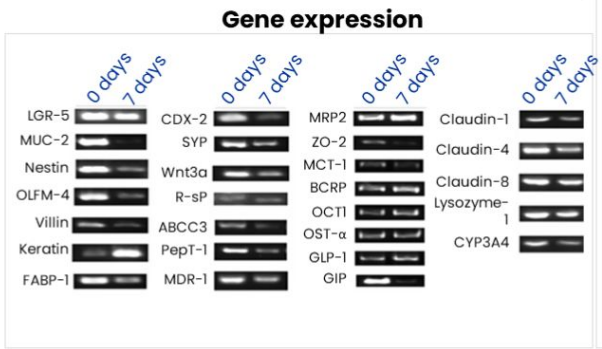
GI tissue architecture and function maintained outside animal





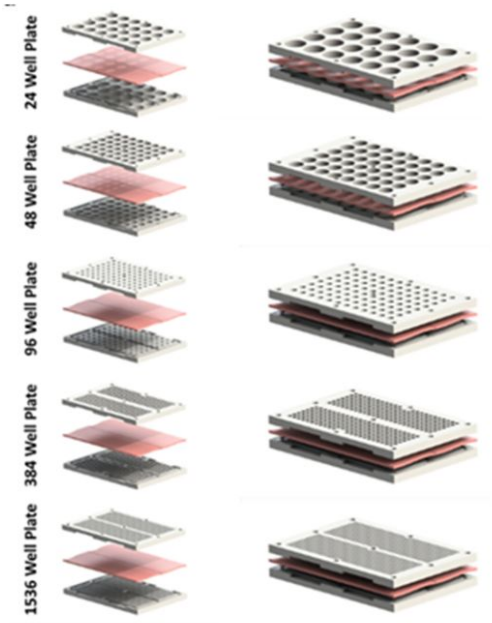






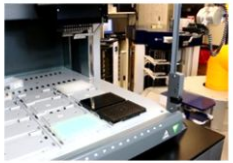
Nature Biomedical Engineering 4, 544–559 (2020)

GI-ORIS™ HTP Absorption Variability Evaluation



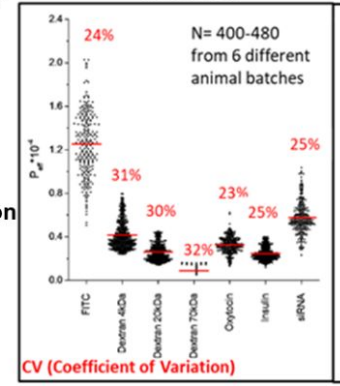
Automated Incubator

Liquid Handling Station

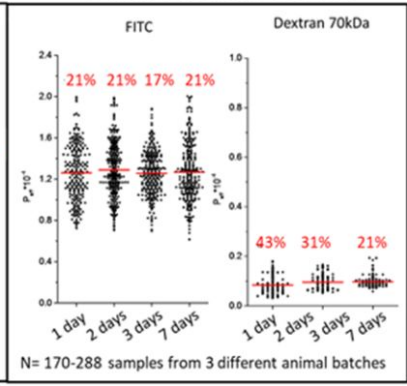


Well plate reader

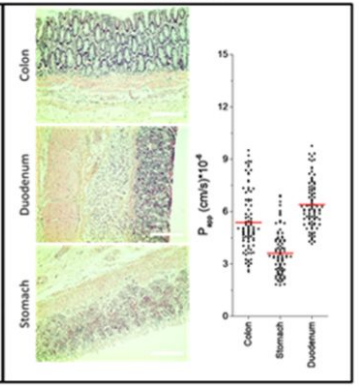
Variability analysis of intestinal absorption



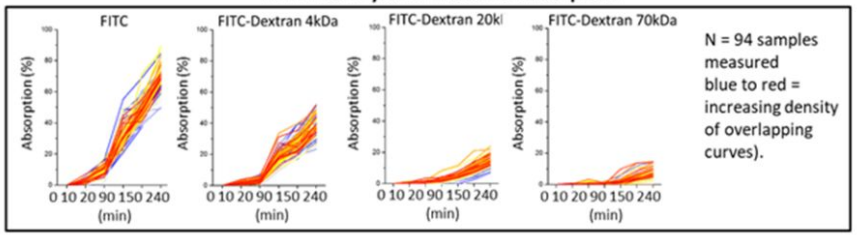
Variability analysis of intestinal absorption re-using same tissue over time



Variability analysis of various GI Segments



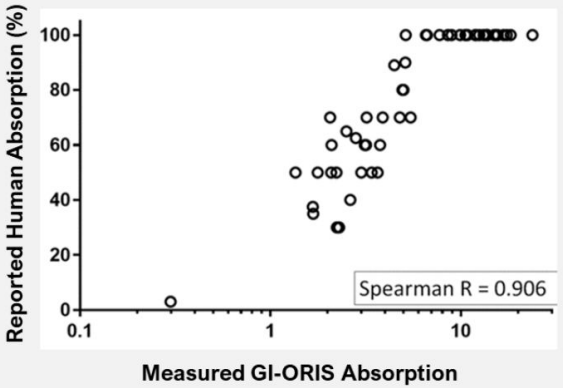
Kinetic analysis of intestinal absorption



Nature Biomedical Engineering 4, 544–559 (2020)

GI-ORIS™ Drug Absorption Prediction

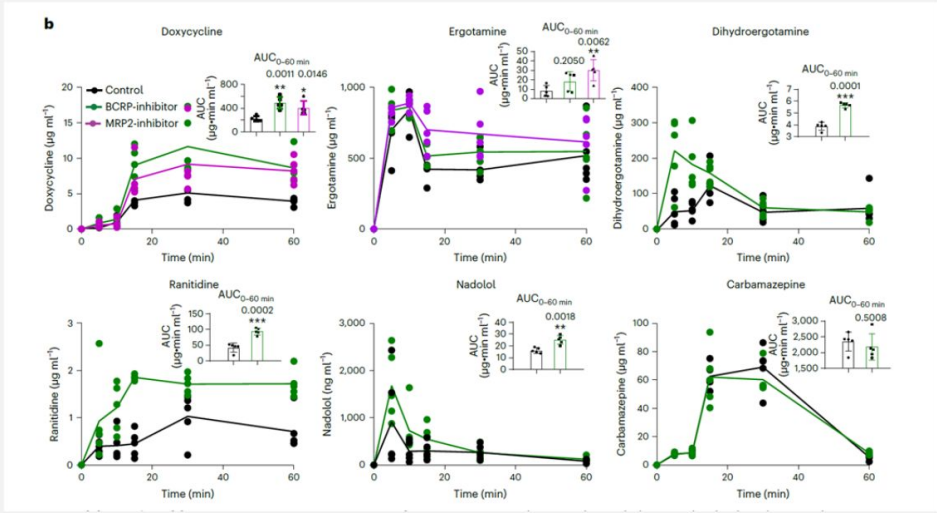
GI-ORIS™ vs. Human Drug Absorption



- Correlation to human absorption established with 60 SMW drugs with known human absorption.
- The GI-ORIS™ system showed excellent
- Caco-2 Transwell System used as benchmark showed R^2=0.3)

Nature Biomedical Engineering 4, 544–559 (2020)

GI-ORIS™ Drug Transporter Prediction

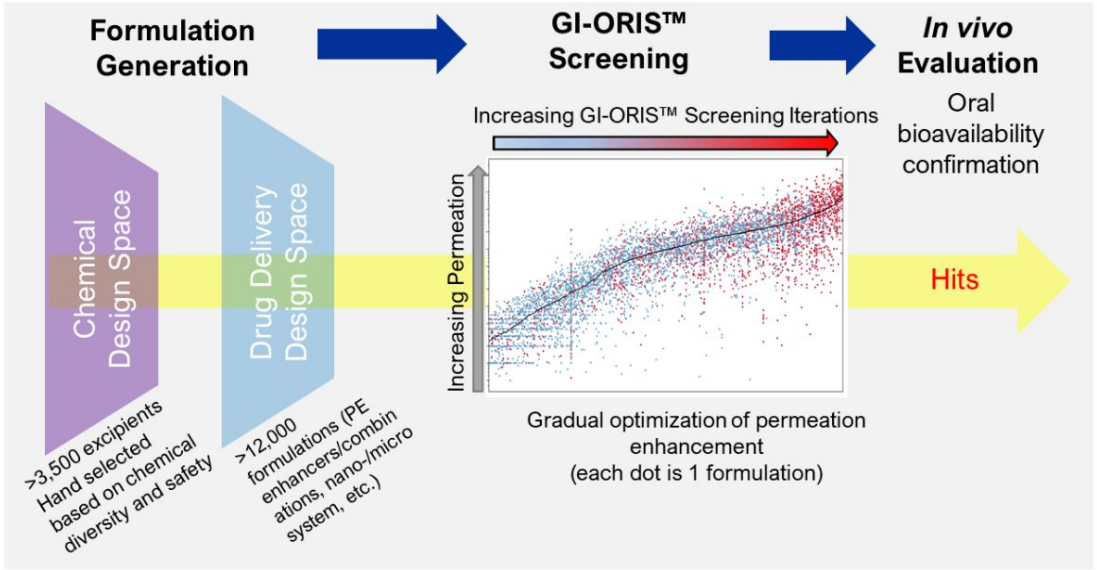


- Comparison in GI-ORIS™ permeability versus in vivo (mice) of different SMW model drugs in presence of transport inhibitors
- Further studies knocked down drug transporters (P-gp, BCRP, MRP2, PEPT1, and MCT1) and established correlation with existing human data.

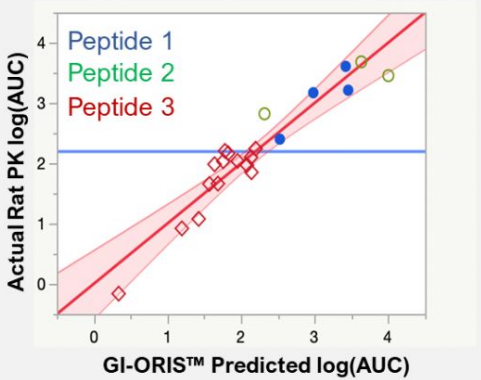
Nature Biomedical Engineering 8, 278–290 (2024)

GI-ORIS™ Formulation/Excipient Screening for Oral Bioavailability Enhancement

GI-ORIS™ Formulation/Excipient Screening Process



GI-ORIS™ to Rat PK

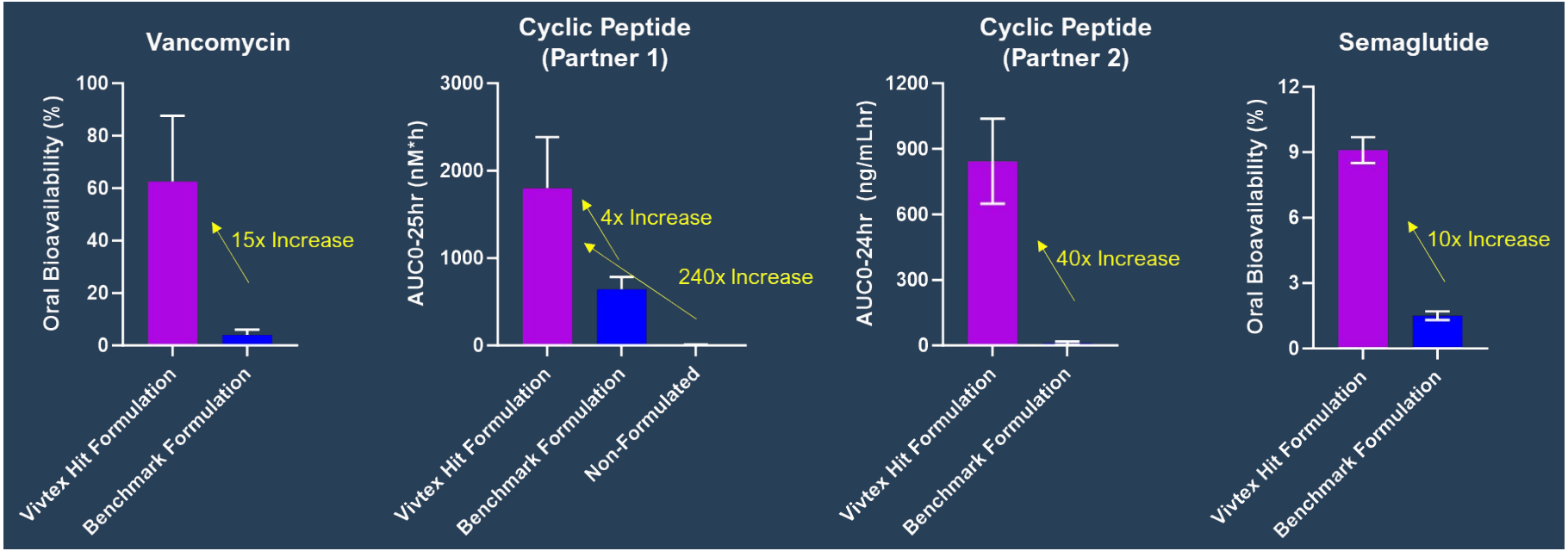


- 21 oral peptide formulations tested
- Excellent in vivo predictability using multiple linear regression

Screening Summary	**Vivtex Data:** >200,000 Data Points	**Number of APIs Screened:** ~ 35 (focus on peptides and oligonucleotides)

GI-ORIS™ Peptide Formulation/Excipient Hits

Case Studies: Evaluation of Oral Bioavailability of Liquid Vivtex Formulations in Rat PK Model



Benchmark is Sodium Caprate (C10) in all case studies

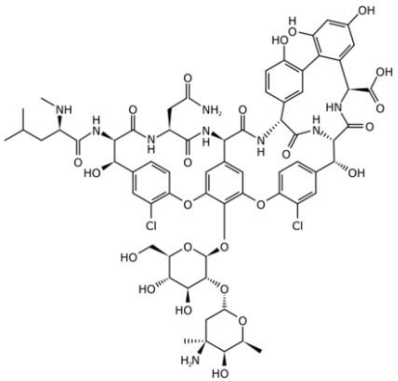
Liquid to Solid Oral Peptide Formulation Translation: Challenge

- Additional layer of complexity with the solid dosage release profile and target GI segment: API and excipient need to release at the same time at the right place
- Historically, solid dosage oral peptide formulation oral bioavailability in large animals has been limited to low single digits (glass ceiling)
- Example:

RYBELSUS®
semaglutide tablets

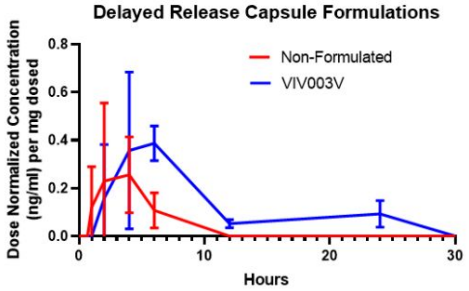
Liquid to Solid Oral Peptide Formulation Translation: Case Study Vancomycin

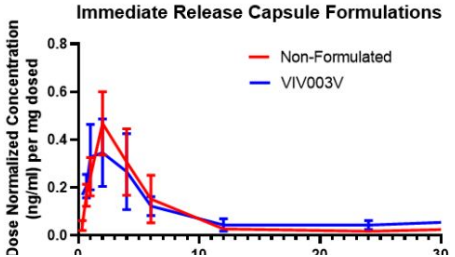
Vancomycin Background



- Tricyclic glycopeptide antibiotic with a molecular weight of 1,449.3 Da.
- Requires IV administration in hospital or outpatient setting.
- For skin and soft tissue infections (SSTIs), there are ~ 650,000 Patients in US alone that receive IV vancomycin.

Vivtex Solid Dosage Formulation 1st Attempt

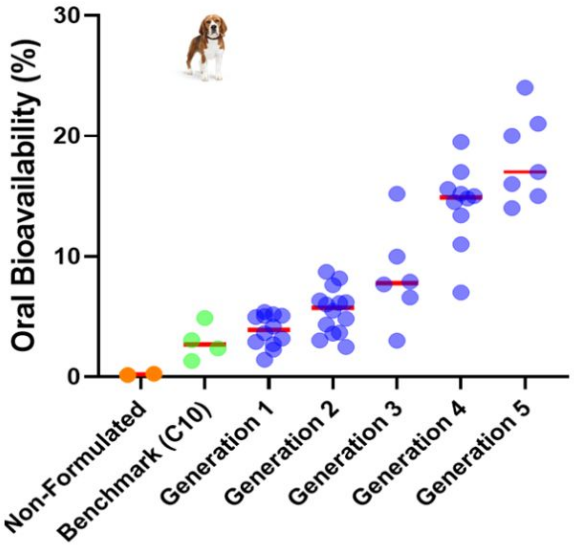




Dog PK results, Error bars represent Standard Error of 3 Dogs per group

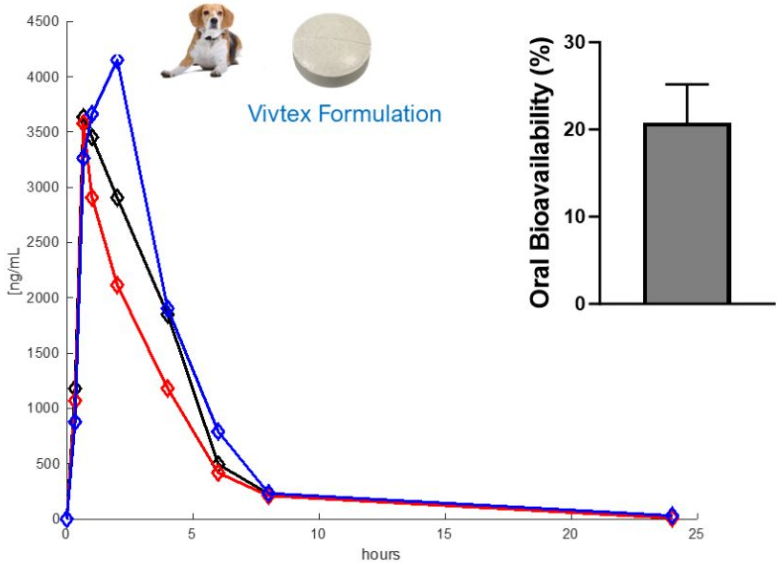
Liquid to Solid Oral Peptide Formulation Translation:
Case Study Vivtex Vancomycin Formulation

Empirical Optimization of Solid Dosage Formulations



Each dot represents one dog PK experiment, red line is mean
Each Generation is a new solid dosage formulation composition

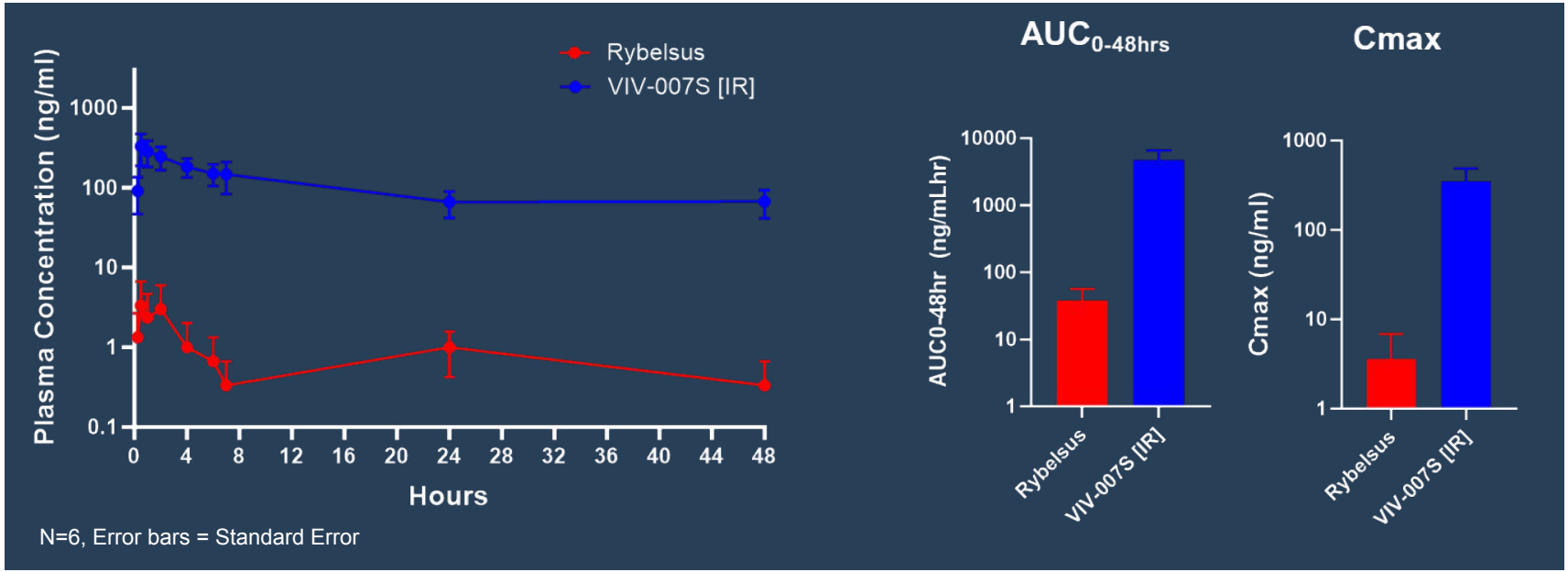
Vancomycin lead Formulation Dog PK Data



~ 7 times higher oral bioavailability compared to Sodium Caprate (C10) in delayed release formulation

Liquid to Solid Oral Peptide Formulation Translation:
Case Study Vivtex Semaglutide Formulation

Generation #2 Vivtex Semaglutide Formulation head-to-head against Rybelsus®

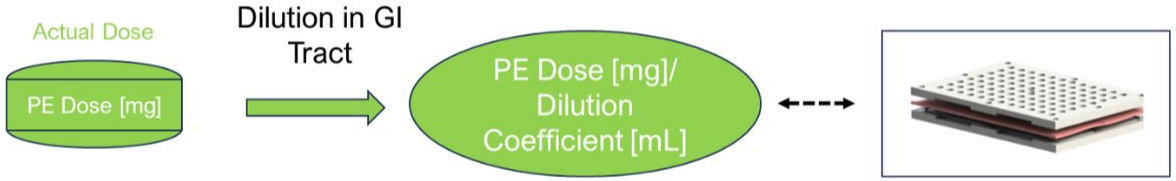


- **VIV-007S [IR]:** Immediate release tablet with mass ~ 500mg
- **Rybelsus®:** Commercially available 14mg strength tablet

How can we accelerate the Liquid to Solid Formulations Translations?

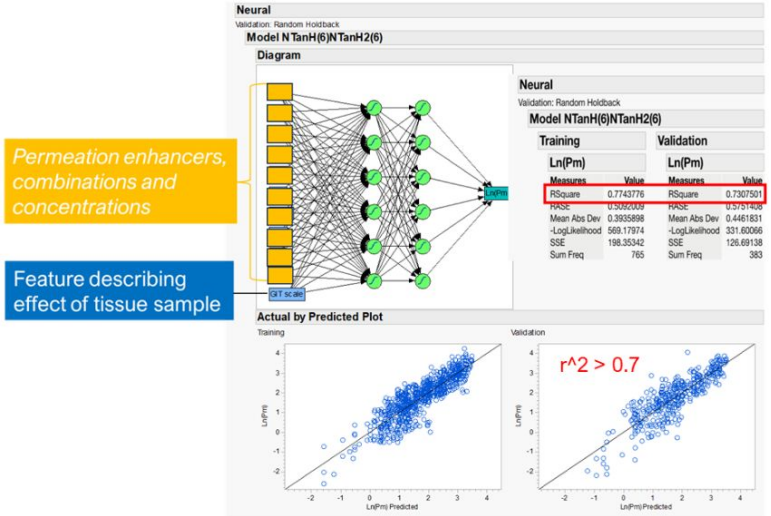
- We assume that liquid formulation concentration equals to the local concentration gradient of a solid dosage formulation composition at the proximity of the GI tissue.

- Can we systematically identify optimal excipient amount and ratio of excipients for permeation of peptide compounds in different GI segments (stomach, duodenum, jejunum, etc.) and different GI conditions (luminal GI environment) to identify how well these formulations might perform in vivo?

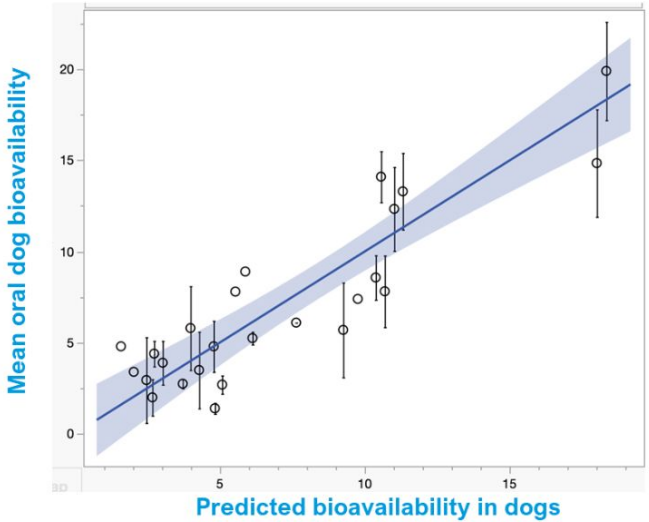


Data Driven Reduction of Solid Dosage Formulation Design Space: Example Vancomycin

Artificial Neural Network (ANN) architecture on 1,400 Vancomycin Permeation Observations



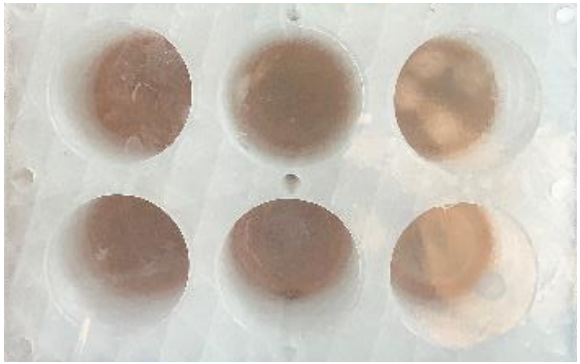
ANN GI-ORIS vs. Oral Dog PK Correlation



63 dog PK bio-availabilities (AUC)
24 different formulations averaged, Error bars are Standard Error

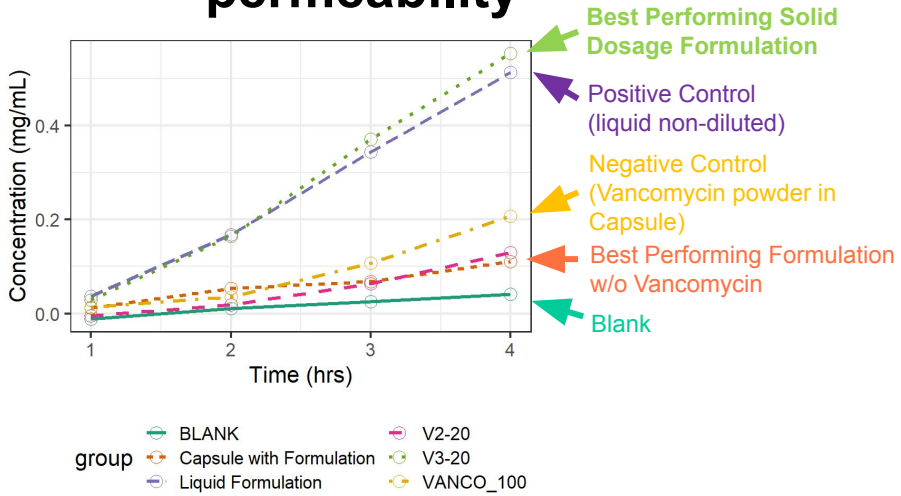
GI-ORIS™ Assay for Solid Dosage Formulation Evaluation: Example Vancomycin

Solid Dosage GI-ORIS™



- Large volume donor chamber GI-ORIS™ wells for solid dosage formulations
- These GI-ORIS™ plates can be put on orbital shaker to incorporate movement

Time course GI-ORIS™ permeability

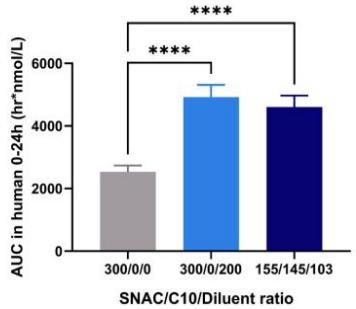


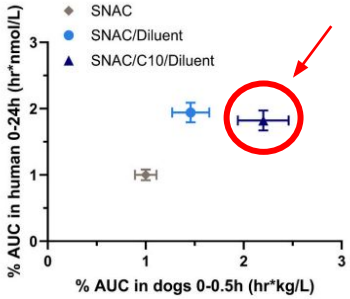
Large animal to Human PK Translation Challenges: Case Study

Oral SNAC/C10/Diluent Formulation for PCSK9 Inhibitor Peptide Evaluated in Dogs and Humans

Table 2
Compositions of the PCSK9 inhibitor tablets for clinical trial. Reference formulations were made with either SNAC only or SNAC/diluent.

PCSK9 inhibitor (mg)	SNAC (mg)	C10 (mg)	Diluent (mg)
40	300	–	–
40	300	–	200
40	155	145	103



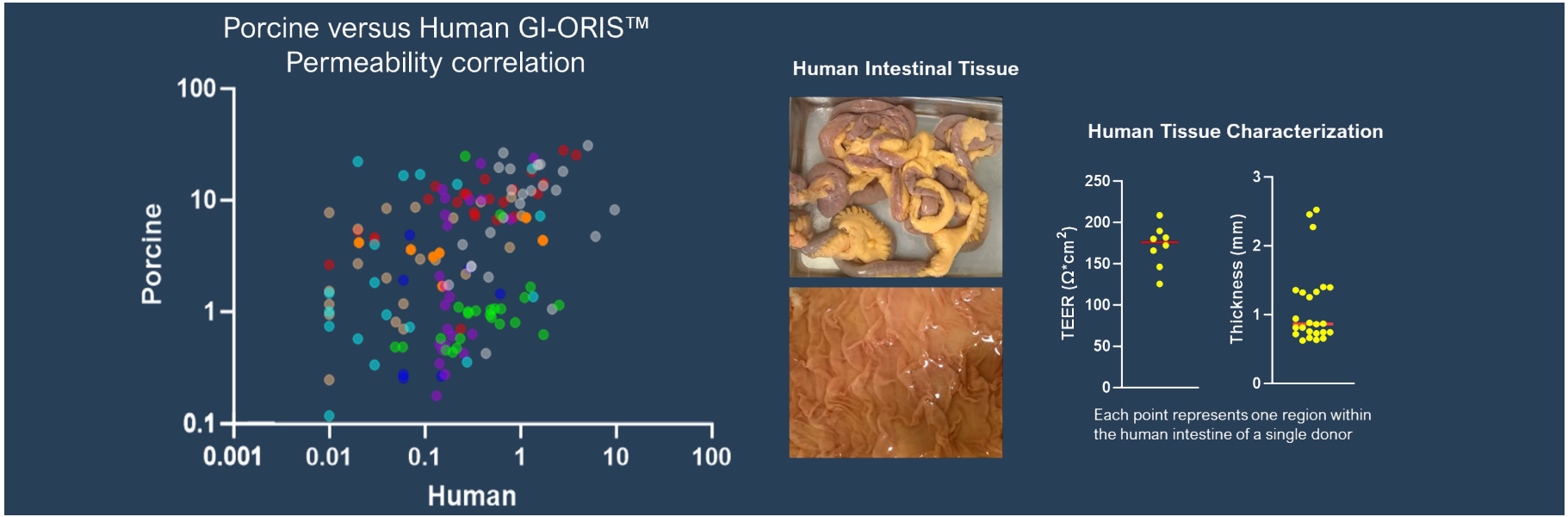


- Observed disconnect between PK exposure enhancement between dogs and humans (IR formulation)
- Observed enhancement effect of SNAC/C10/diluent formulation in dogs did not translate in humans.

Journal of Controlled Release 378 (2025) 92–102

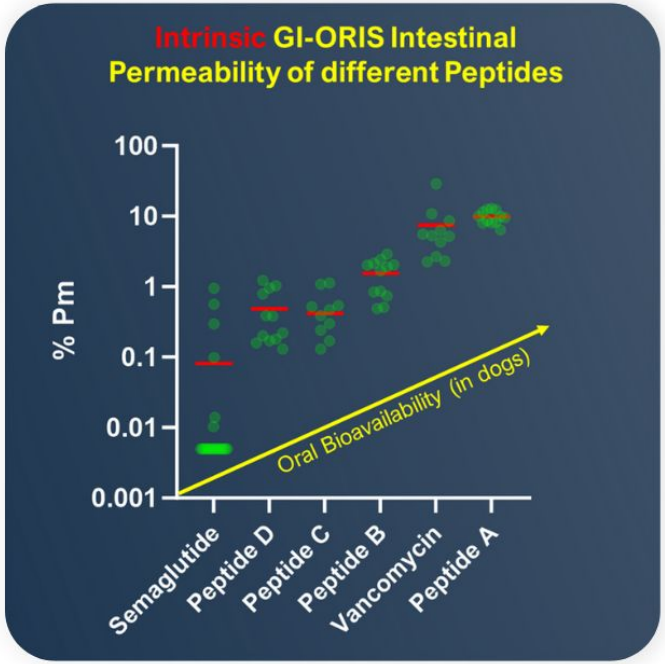
Large animal to Human PK Translation Challenges:
GI Tissue Permeability Differences using GI-ORIS™ assay

Human vs. Porcine GI Permeability of different Peptides

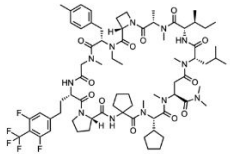


Each color is a different compound; Each dot is the averaged permeability an individual formulation
All compounds are different peptide therapeutics except red dots represent an antisense oligonucleotide

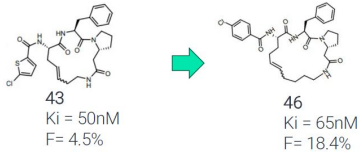
Intrinsic vs. Formulation enabled Peptide Intestinal Permeability: Non-formulated Peptide



- **Intrinsic intestinal permeability of peptides varies by orders of magnitude**
- **De novo design of orally bioavailable peptide compounds can result in high oral bioavailability:**

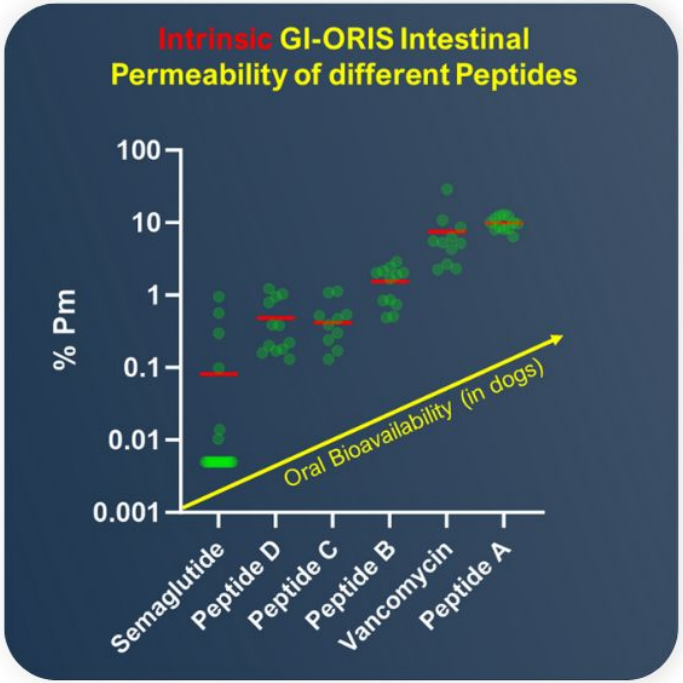


Luna 18 (11mer with ~20% oral bioavailability)
Chugai
J. Am. Chem. Soc., July 18, 2023

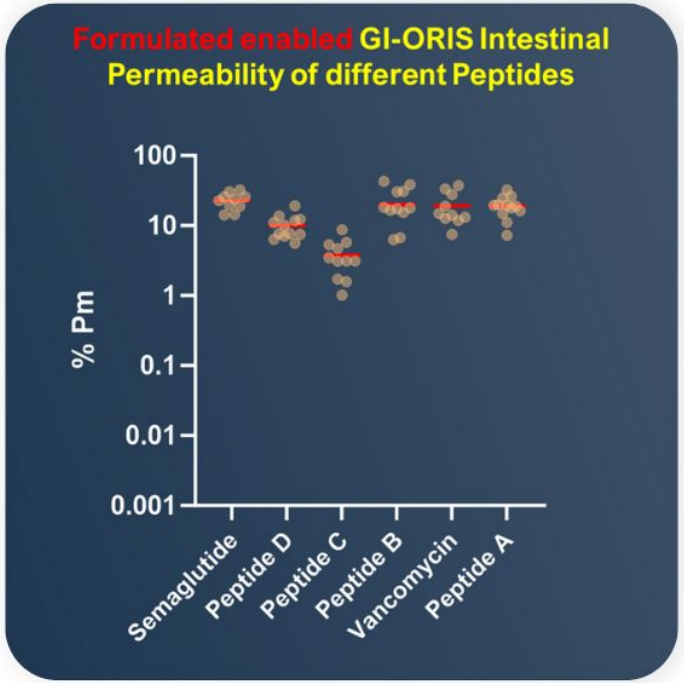


nCycle (11mer with ~18% oral bioavailability)
Orbis Medicines
Nature Chemical Biology, 20, 624–633 (2024)

Intrinsic vs. Formulation enabled Peptide Intestinal Permeability: Formulation Enabled



Custom Formulations through GI-ORIS screening



Conclusion

- HTP GI Tissue permeability screening enables identification of new formulations that outperform currently available permeability enhancers.
- Key challenge remains the translation from liquid formulation concepts into viable solid dosage formulations.
- Ways to derisk challenges in large animal to human PK translation through specific in vitro/ex vivo assays.
- Rapid advancements in de novo design of peptides with high GI tissue permeability, which can be further leveraged by introducing custom formulations.