ALTIS BIOSYSTEMS

The Development of a 96-well Plate-Based Model of the Human Intestinal Epithelium with Applications for Modeling Toxicity and Pharmacokinetics

October 2023

Altis Biosystems

Located in **Research Triangle Park** in Durham, NC

- Founded by the Allbritton and Magness Labs
- ~7,000 ft^2, full-service laboratory, and administrative space
- Equipped with state-of-the-art analytical instrumentation

20+ Full-Time Employees

- Launched in 2017 with 3 employees
- 10 PhDs across the company

Dedicated Scientific Teams

- Cell Operations Team
- Quality Control
- R&D Team
- Commercial Services Team

THE NEED

Developing next-generation human intestinal primary cell models

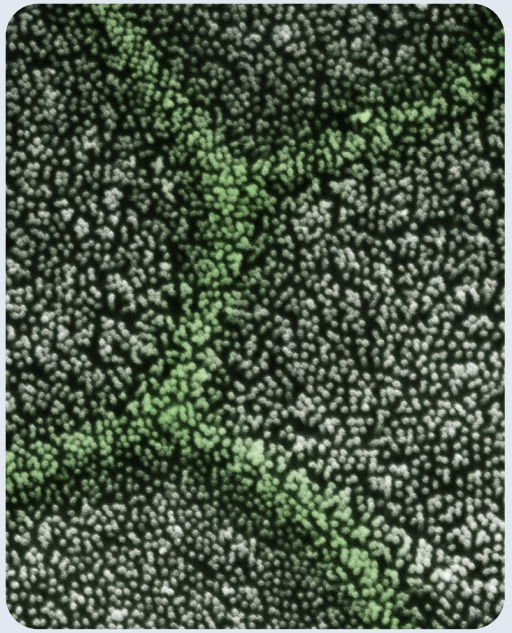
Scale and Quality:

- Donor and tissue diversity
- Commercial scalability
- Quality control and reproducibility

Assay Development:

- "Fit-for-Purpose" design
- Model complexity and scale matched to throughput requirement
- Qualification/Validation

Platforms needed to correctly model human GI biology



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A unique library of stem cells from multiple donors

For each donor, the BioBank has:

Full-length intestinal tissue from healthy, transplant-grade donor intestine

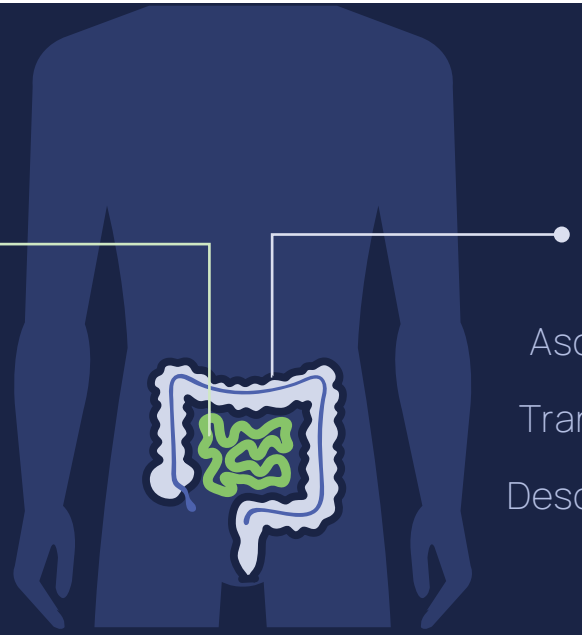
- Epithelial stem cells isolated from all regions of the small intestine and colon

Diverse Demographics

- Male, Female
- Caucasian, African American
- Range of ages, BMI, etc.

Stem cells expanded in culture to produce **commercial-scale cell lots**

- Test on the same donor &/or region over time
- Cells retain native properties without genetic or phenotypic drift
- Rigorous QC conducted on each lot



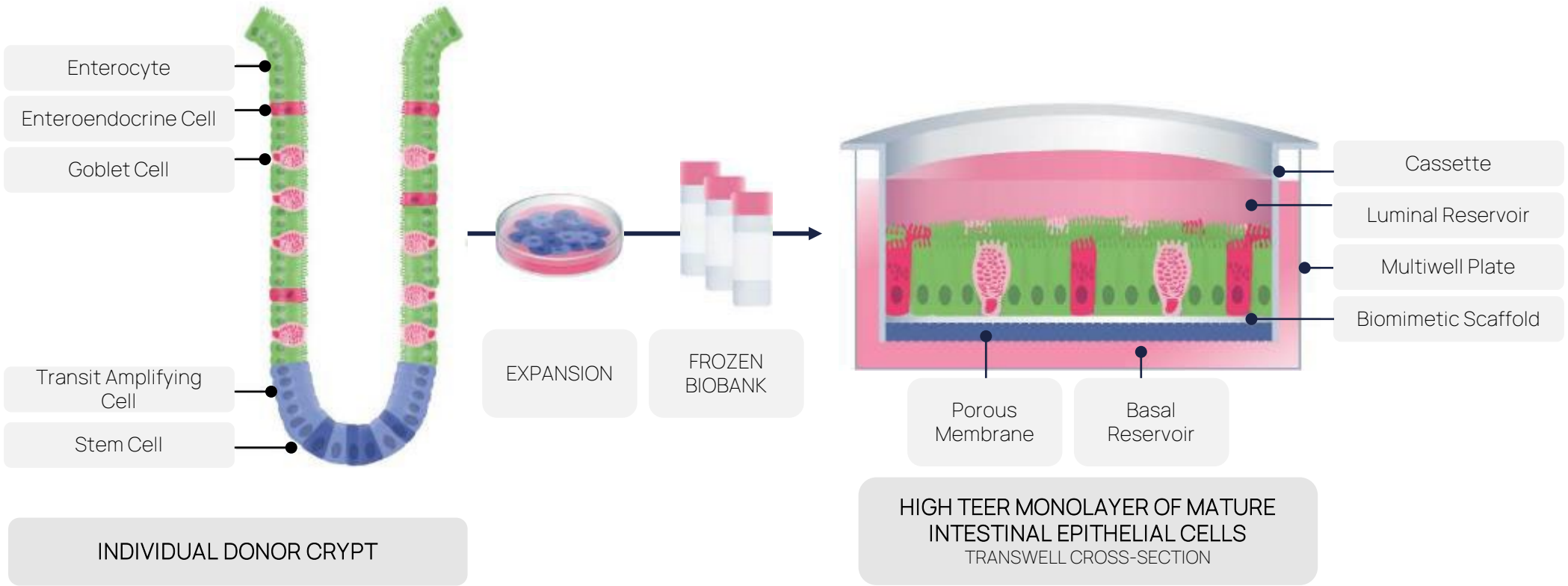
Small Intestine

- Duodenum
- Jejunum
- Ileum

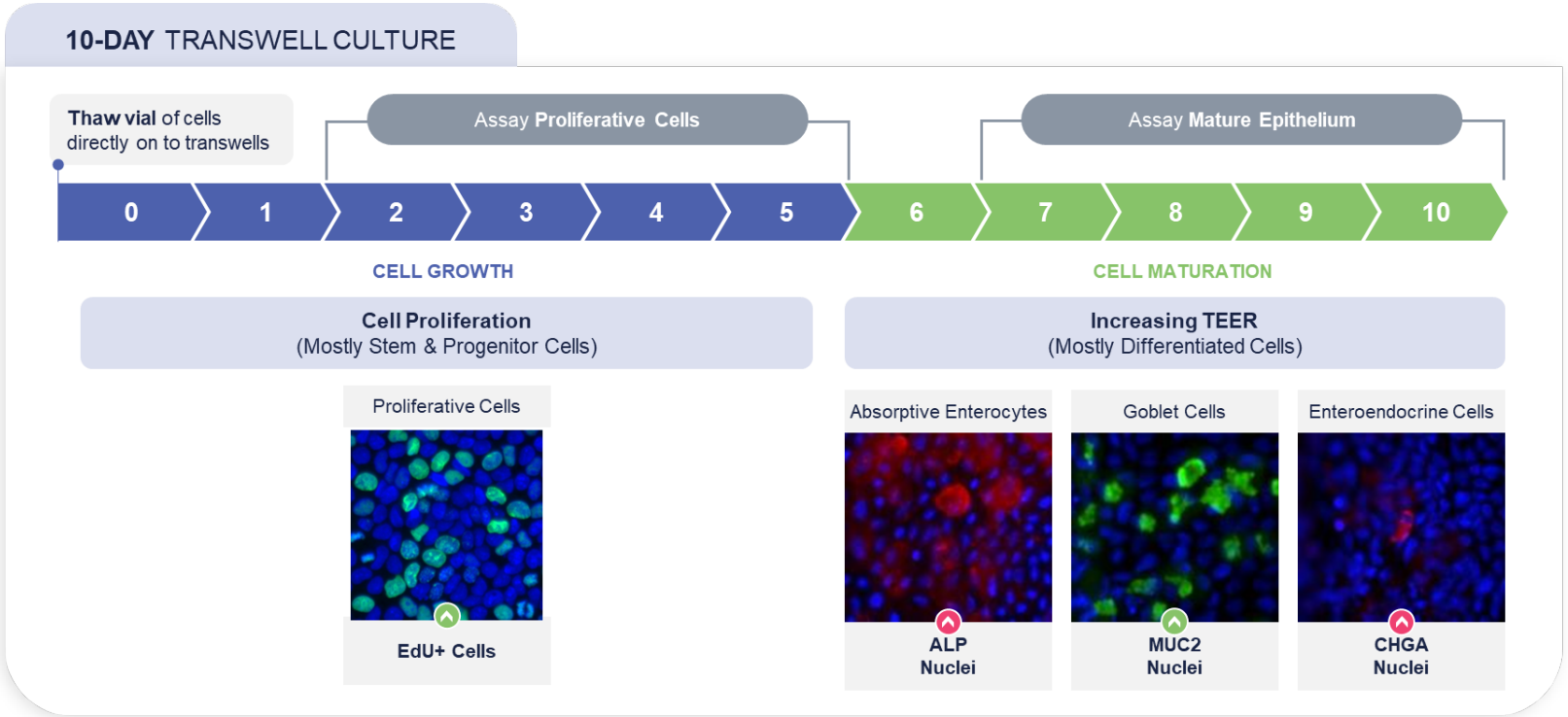
Colon

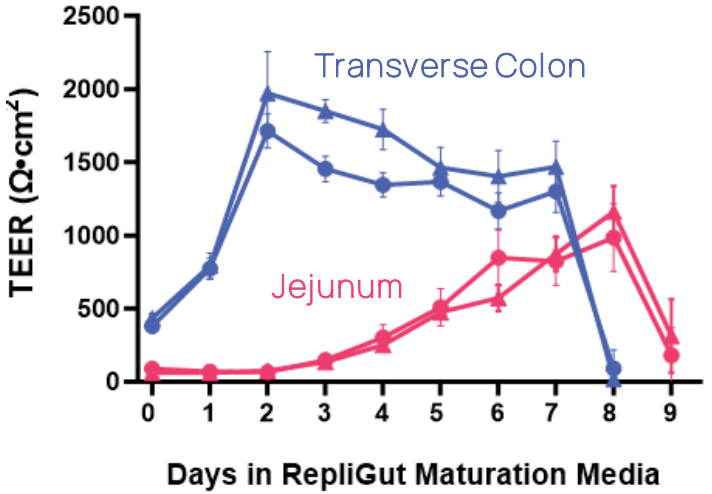
- Ascending Colon
- Transverse Colon
- Descending Colon

RepliGut® platform mimics the cellular composition of the native intestine.

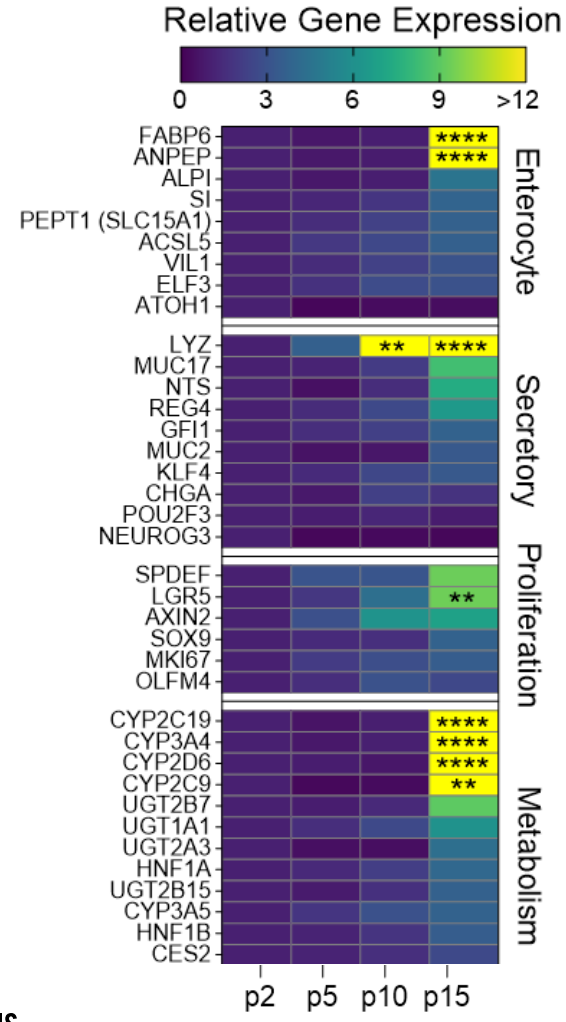


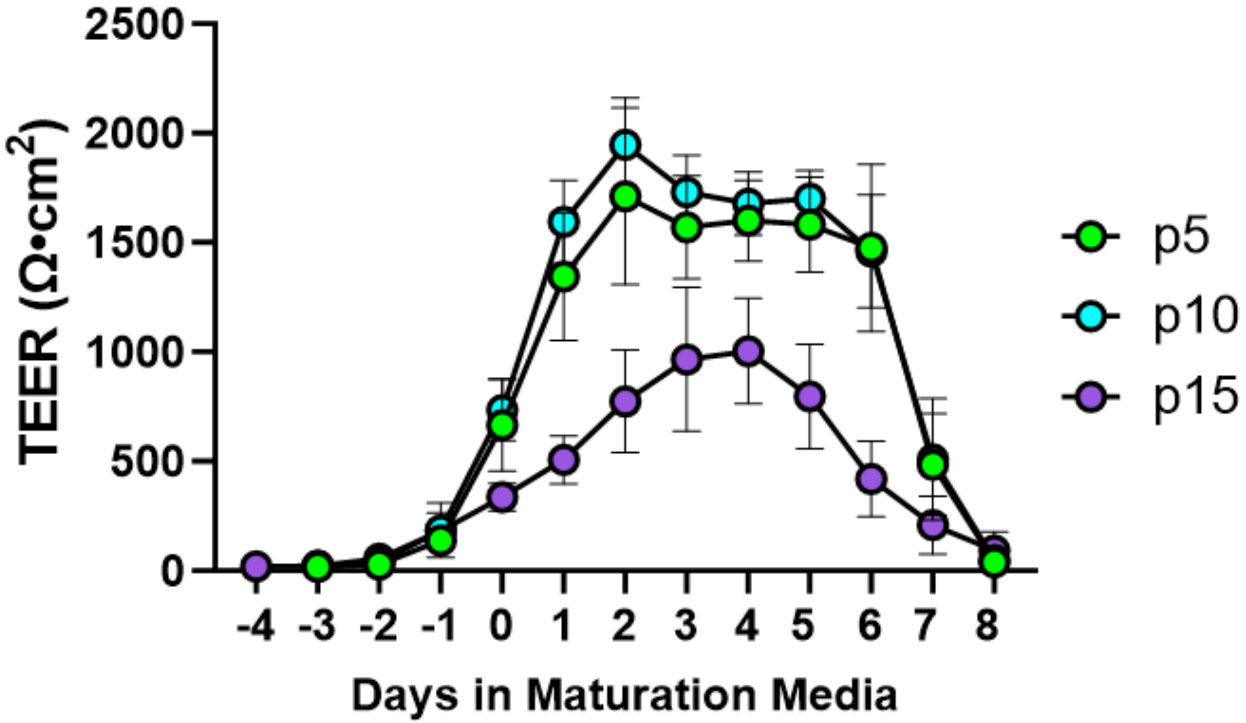
RepliGut® Planar platform replicates the entire life-cycle of the GI epithelium





Phenotypic stability as a function of passage number

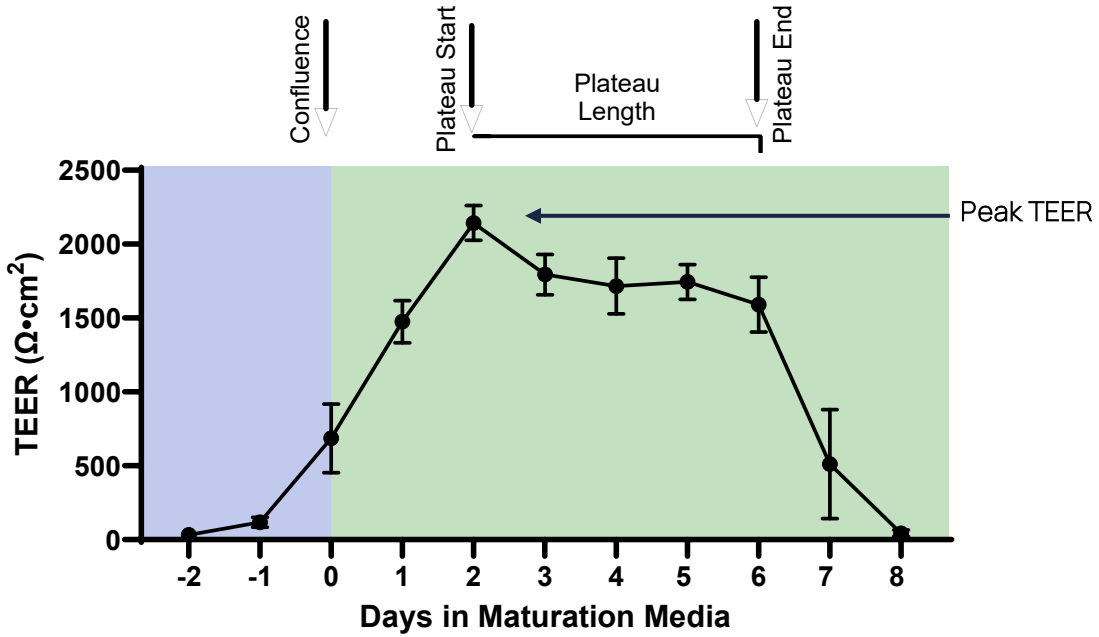




QUALITY

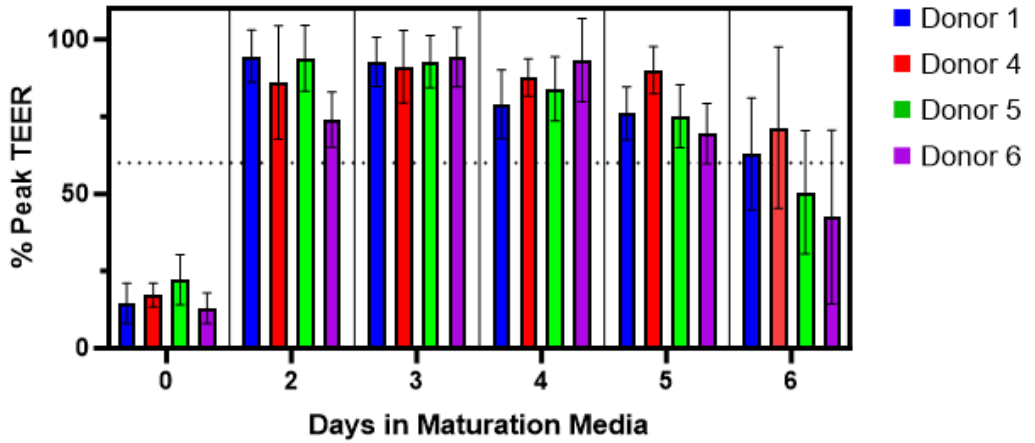
Establishing Standardized Quality Control for commercialized cell lot production

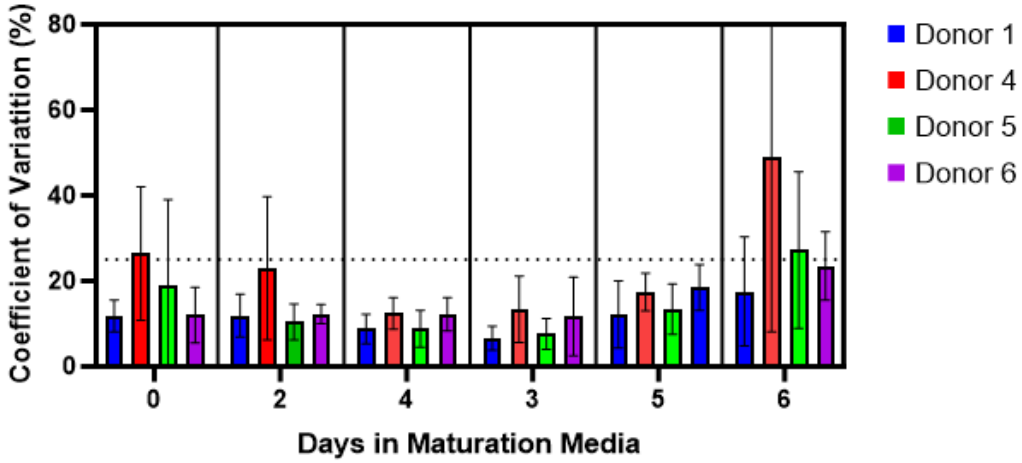
Key quality metrics



- Cell Count
- Cell Viability
- Cytokine response

QC metrics established over >50 independent QC run





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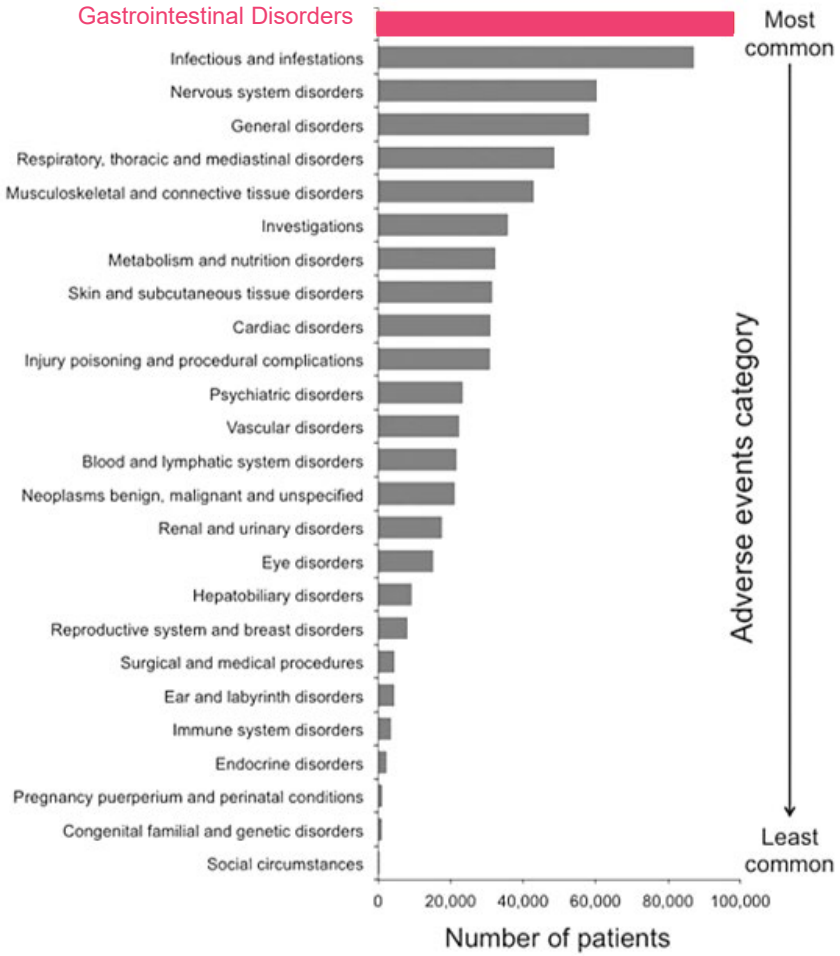
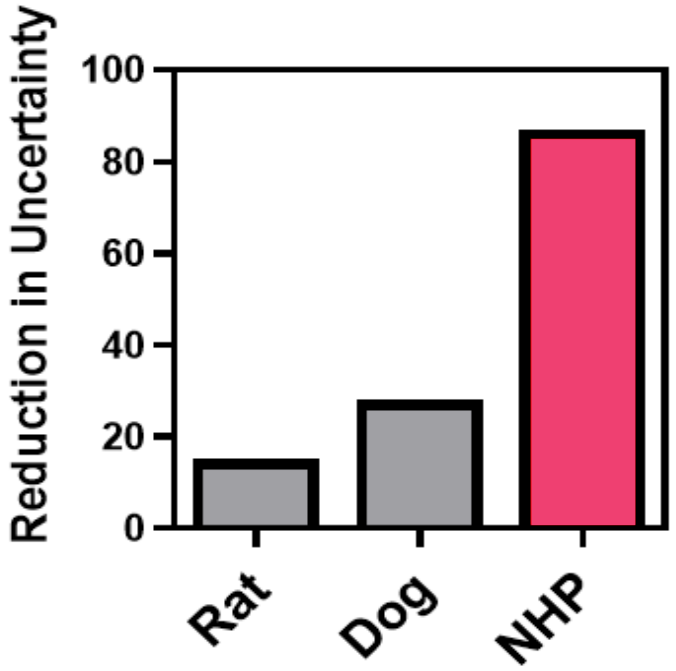
Need in the field for improved GI Toxicology Modeling

GI Disorders are the Most Common Clinical AEs



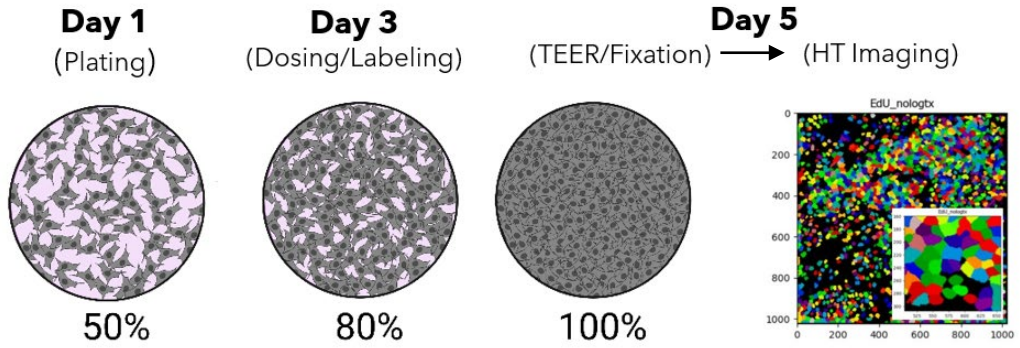
Human GIT predictability vs species



References:
Big Data Mining and Adverse Event Pattern Analysis in Clinical Drug Trials (2016) PMID: 27631620

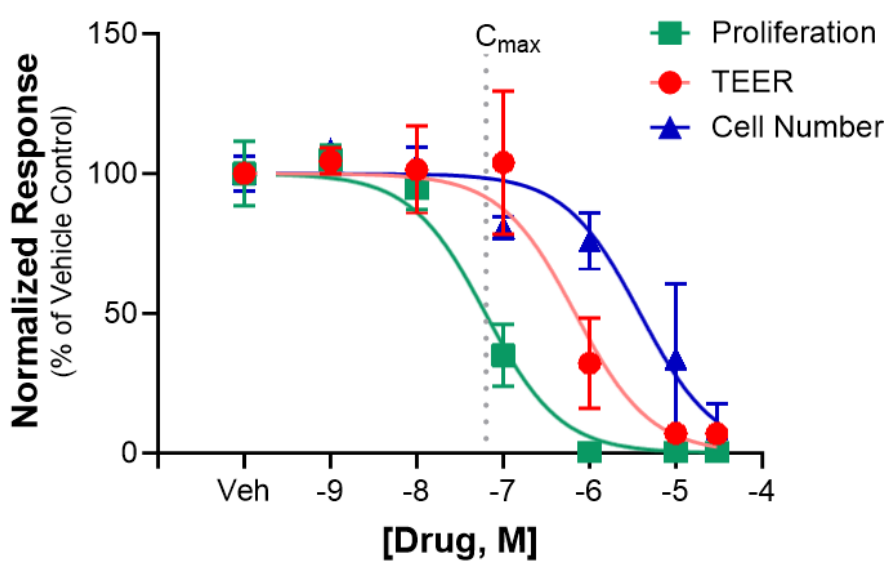
Current nonclinical testing paradigm enables safe entry to First-In-Human clinical trials (2017) PMID: 28893587

Leveraging dynamic culture conditions to establish a simple 96-well plate toxicology assay



Downstream Analyses:

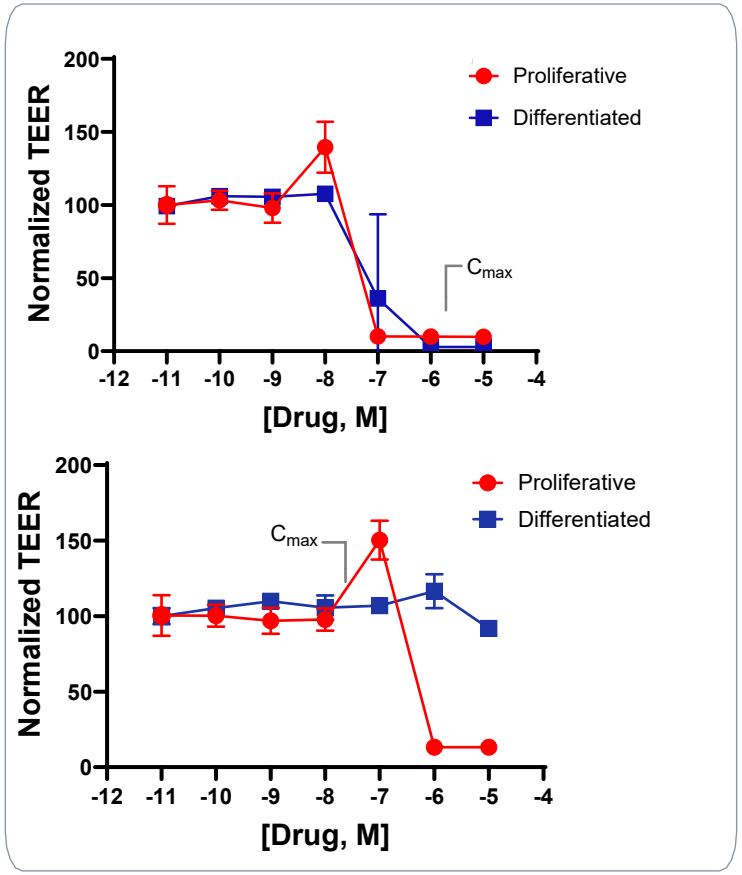
- TEER: Barrier Formation
- DAPI: Total Cell # (Viability)
- EdU: Proliferative Cell #



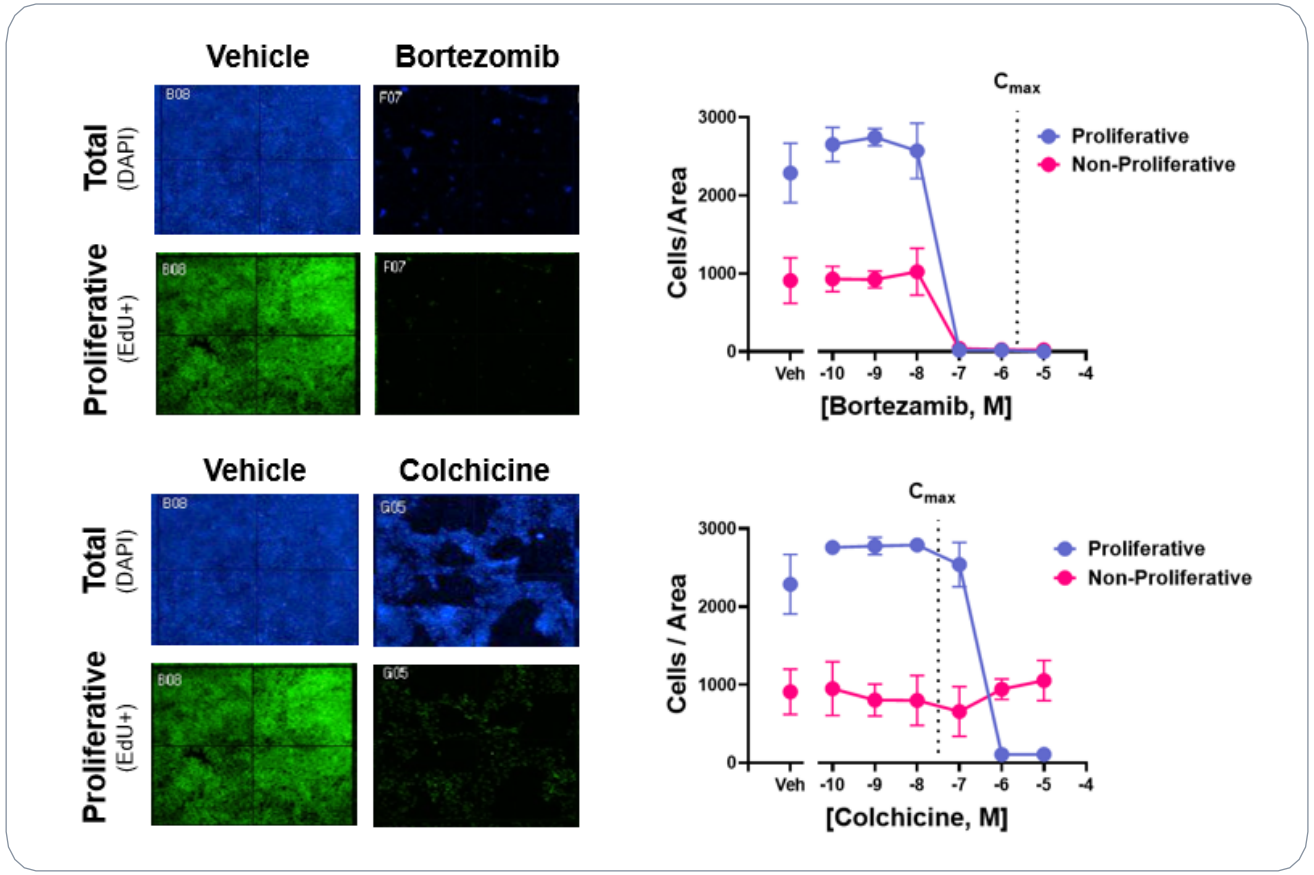
Assay can distinguish underlying Mechanisms of Toxicity

Barrier Formation

Anti-Proliferative Non-Specific



Intestinal Self-Renewal (Proliferation)

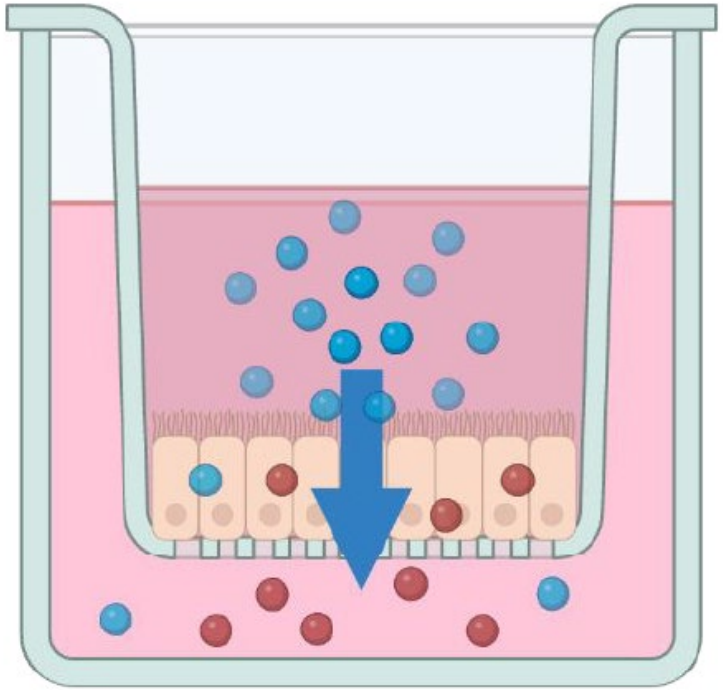


Towards Toxicology Prediction
(IQ Reference Compounds)

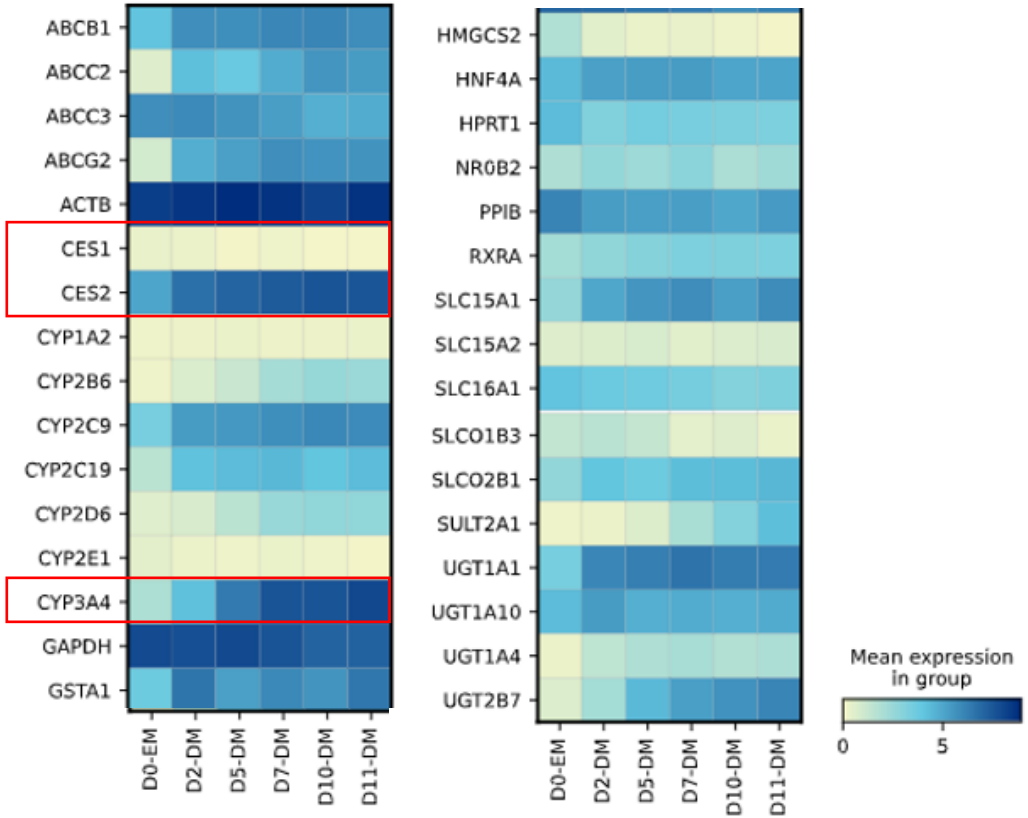
In Vitro IC_{15} / Clinical C_{max}
‹20-fold (Positive); ›20-fold (Negative)

	Compound (Mechanism)	Diarrhea Incidence	Clinical Cmax	RepliGut® (TEER IC_{15})
Positive	**Bortezomib** (Proteosome Inh)	**77%**	**1.3E-06**	**0.01**
Positive	**Colchicine** (Microtubule Inh)	**96%**	**1.8E-08**	**0.04**
Positive	**Afatinib** (EGFR Inh)	**72%**	**7.8E-08**	**1.24**
Positive	**Idarubicin** (DNA Intercalation)	**51%**	**8.8E-08**	**1.36**
Positive	**Docetaxel** (Microtubule Inh)	**42%**	**3.7E-06**	**7.22**
Negative	**Nadolol** (Beta Blocker)	**0%**	**430 nM**	**>25.0**
Negative	**Verapamil** (Ca2+ Channel Inh)	**2%**	**99 nM**	**>100**

Towards establishing formal DMPK Modeling

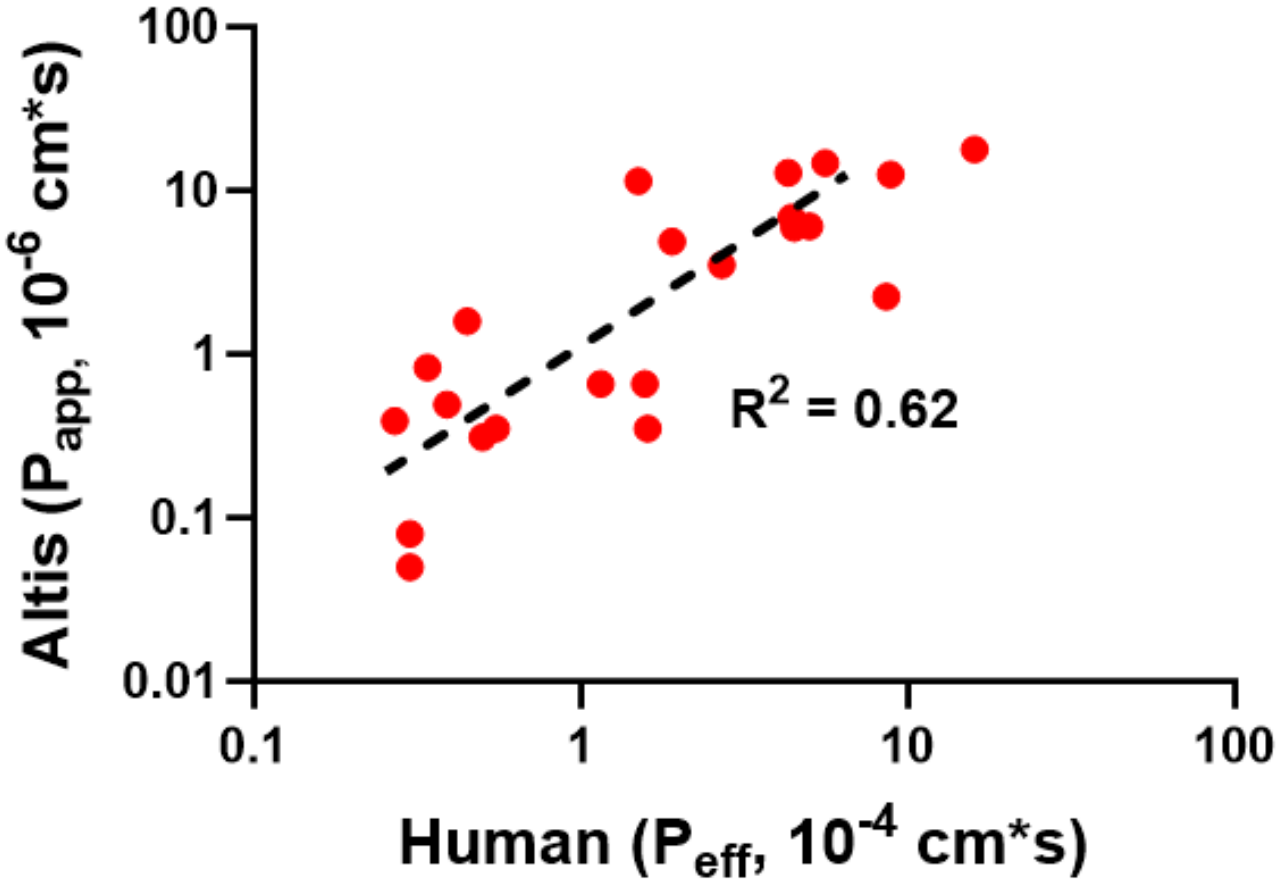


Transcriptomic Profiling
(Relevant Transporters and Metabolic Enzymes)



Towards functional DMPK Testing

Intestinal Drug Absorption (A→B)
(RepliGut® *in vitro* vs Human Clinical data)



Amoxicillin	Budesonide
Antipyrene	Fenofibric Acid
Atenolol	Fexofenadine
Carbamazepine	Ipsapirone
Cephalexin	Lisdexamfetamine
Desipramine	Nifedipine
Ketoprofen	Rivastigmine
Lisinopril	Digoxin
Metoprolol	Fluvastatin
Ranitidine	Losartan
Terbutaline	Enalapril Maleate
Verapamil	Theophylline

Genentech
A Member of the Roche Group

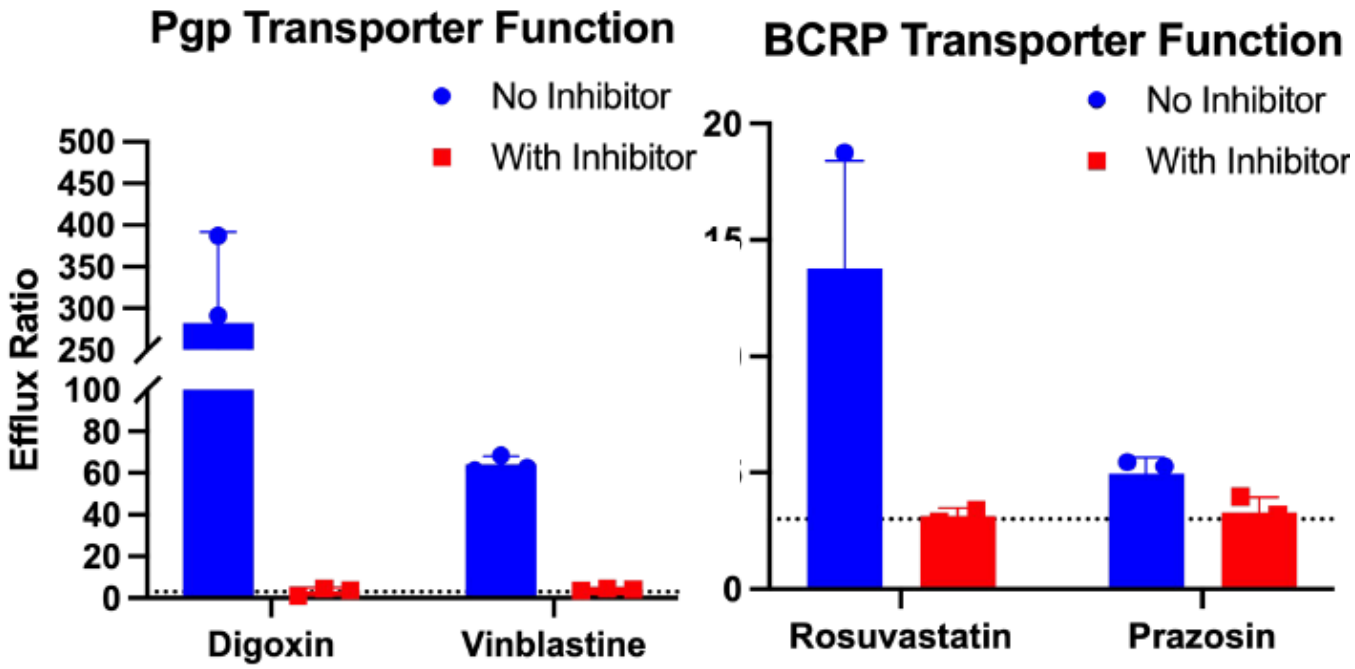
Towards functional DMPK Testing

Measured Quantitative Intestinal Drug Absorption and Efflux

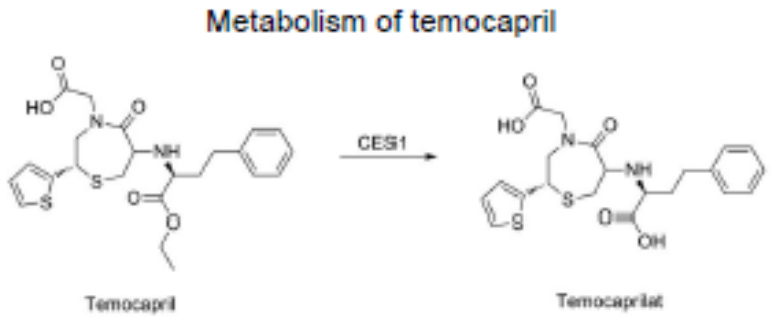
- Passive drug absorption
- PGP- and BCRP-mediated efflux
- PEPT1-mediated peptide transport

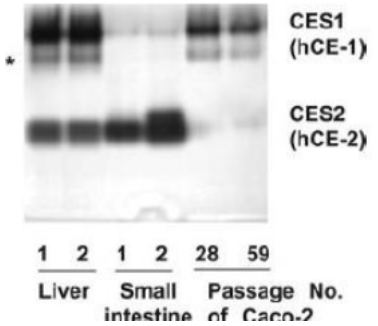
Characterized Functional Drug Metabolism

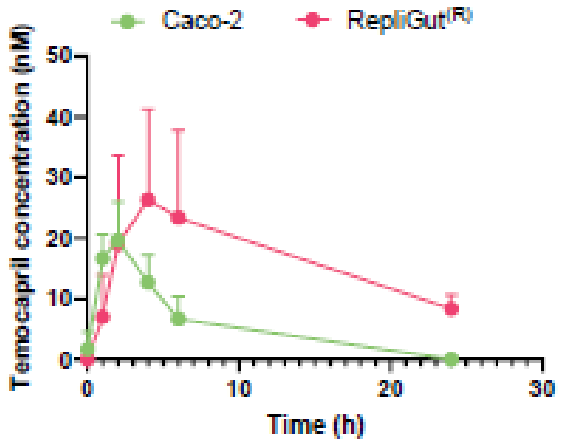
- CYP-enzymes (CYP3A4 & CYP2C2)
- UGT-enzymes (UGT 1A1 & 1A8-10)
- Esterase-enzymes (CES1 & 2)

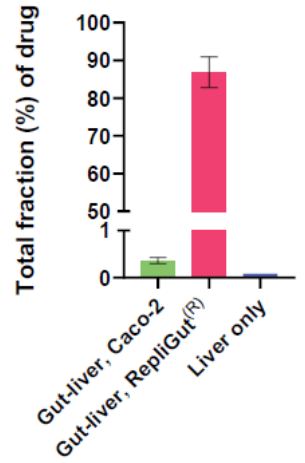


A Gut-Liver Model to predict Oral Bioavailability









Thank you!

National Institutes of Health

- SBIR Support from NIDCR and NCATS

Altis Biosystems team

Industry Collaborators

- Genentech-Roche
- CN-Bio
- AstraZeneca

Academic Collaborators

- Nancy Allbritton Lab (UW-Seattle)
- Scott Magness Lab (UNC-Chapel Hill)

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