Advancing Generic MR Product Development Using Tiny-TIM*sg* to Predict *In Vivo* Performance

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Outline

- **Background**
- **TIM Technology Platform**
- **Case Studies**
  - Pediatrics
  - Coadministration Proton Pump Inhibitor
  - Food Effect
- **TIM-PBBM**
- **Summary**
- **Concluding Remarks**

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Background

Regulatory Trend

Towards animal-free drug development

1938
Animal testing mandated for new drug development

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

2010
3Rs Principle
Develop and **R**efine innovative alternative approaches to **R**educe and **R**eplace animal testing

Food and Agriculture Organization of the United Nations

2013
Expert consultation concludes *in vitro* models should be explored for studying protein quality, i.e. DIAAS

FDA

2022
Modernization Act 2.0
Contesting mandatory animal use (Act 1.0)

FDA

2024
Modernization Act 3.0 Reduce animal testing by promoting and expediting alternative nonclinical testing methods.

LATEST NEWS

April 10, 2025

FDA Announces Plan to Phase Out Animal Testing Requirement for MAb and Other Drugs

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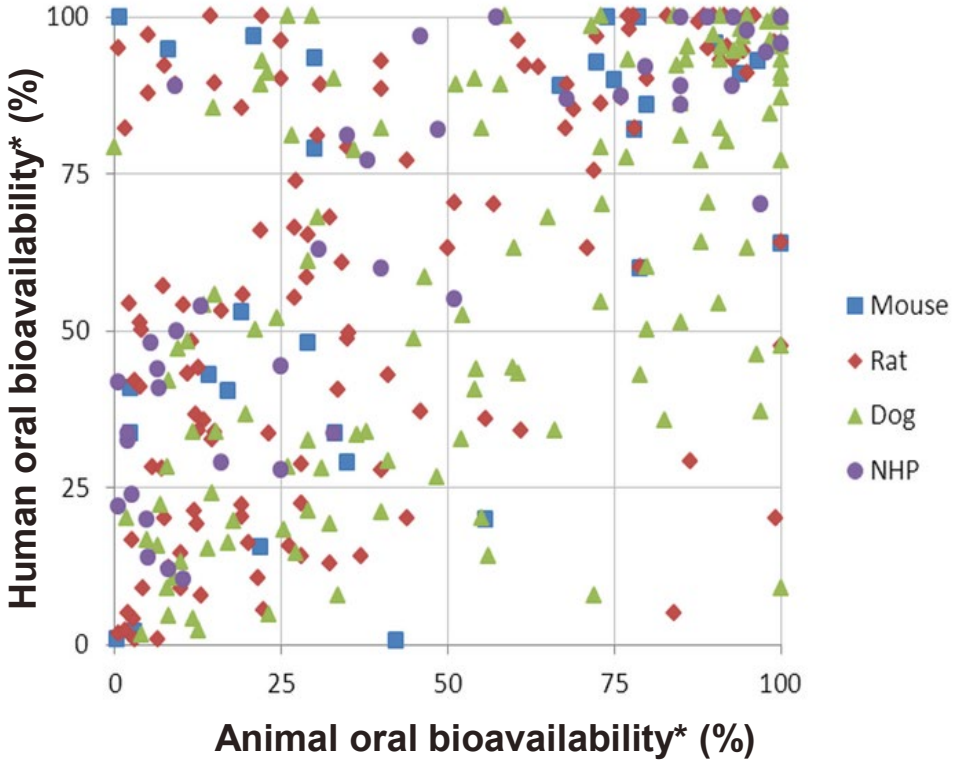
Animals offer a suboptimal “default”

Poor correlation between animal models and humans

- Animals are not strong predictors of human results
- Comparison of 184 compounds between humans and animal models oral bioavailability

Model	Correlation [%] with human bioavailability
Mouse	25
Rat	29 – 46
Pig	36
Dog	37
Coin flip	**50**
Non-human primate (NHP)	69
TIM Technology	**84 – 99**



* % of dose found in bloodstream

Musther et al., 2014, Henze et al., 2018, Deglaire et al. 2009, Rowen et al.1994, Bodwell et al. 1980, LaPlace ~17th century

Predicting *in vivo* behavior of MR formulations is challenging

Significant impacts of:

Excipients (polymeric or other)

Interplay of entire formulation with dynamic GI lumen conditions

Hydrodynamics (mixing, shear and normal forces acting on the formulation)

Exposure to most diverse GI conditions (stomach to caecum / colon)

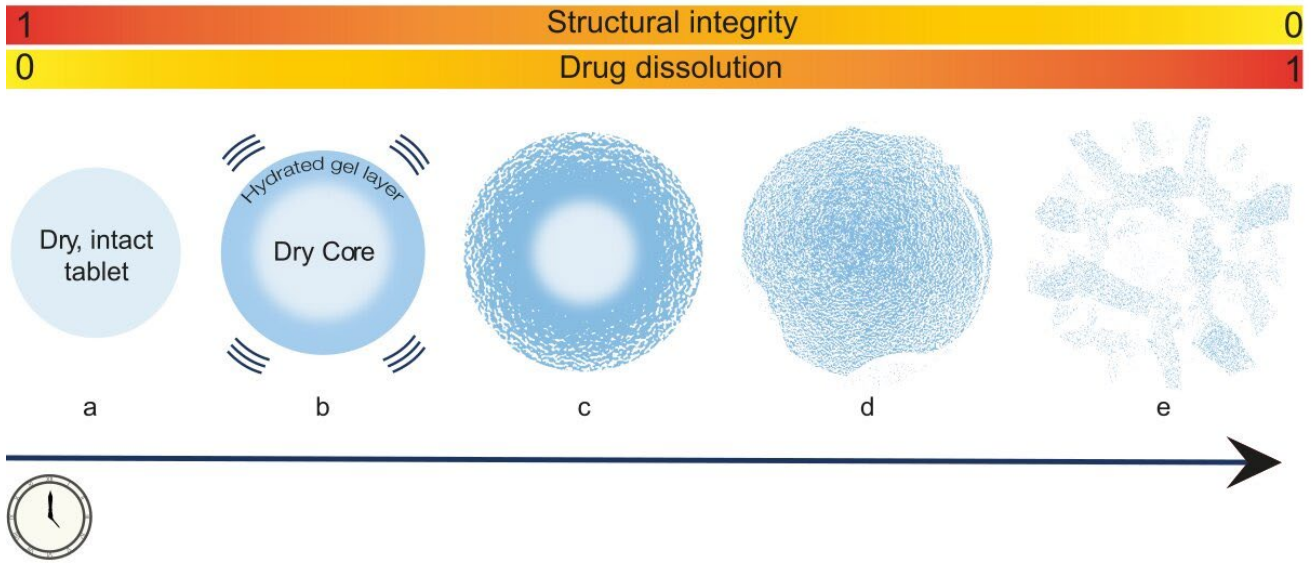


Image by Connor O'Farrell

The TIM Technology Platform

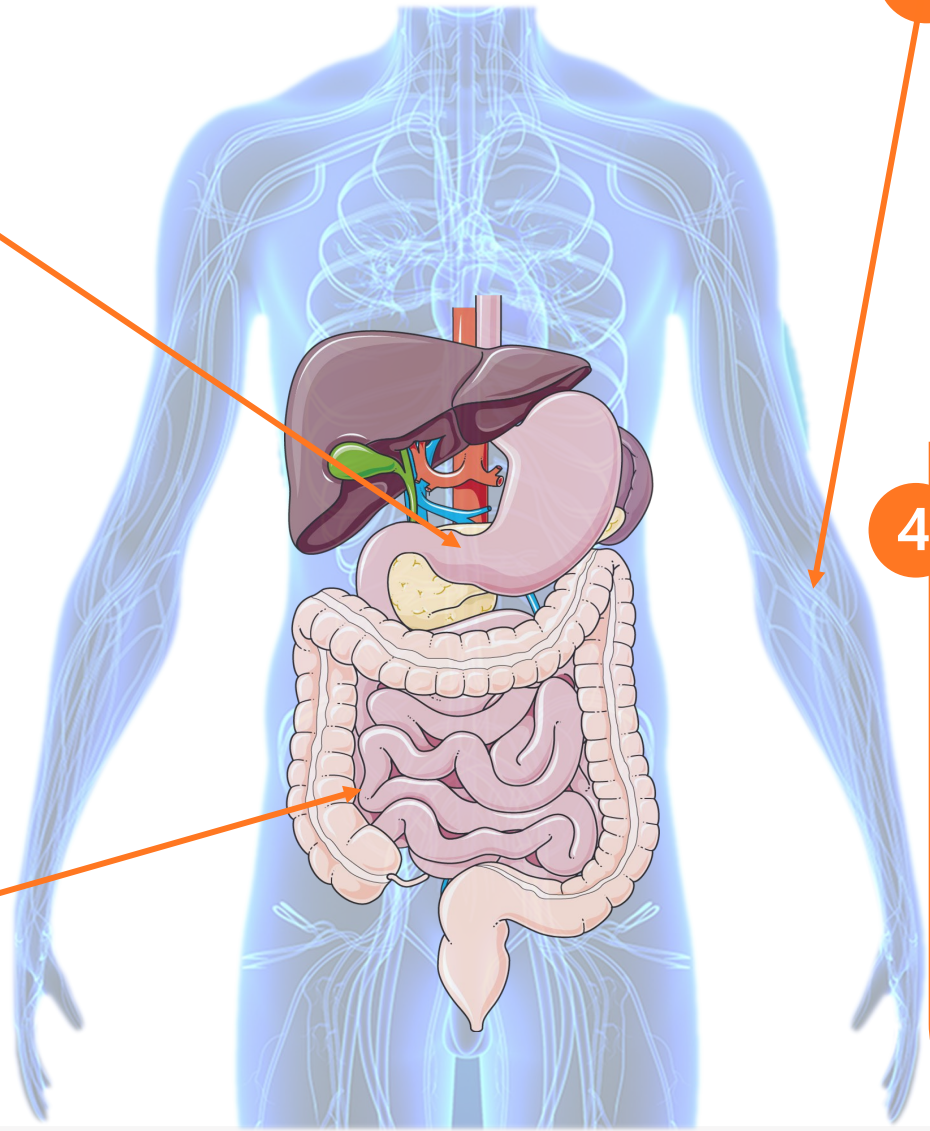
The TIM Technology Platform

The Intestinal Models

1

Drug release & dissolution

- *In-vitro* stomach + small intestinal model
- *In-vitro* large intestinal model



Biological Twin of Gut Wall

2

Drug Permeability & Absorption

3 Digital Twin of Human

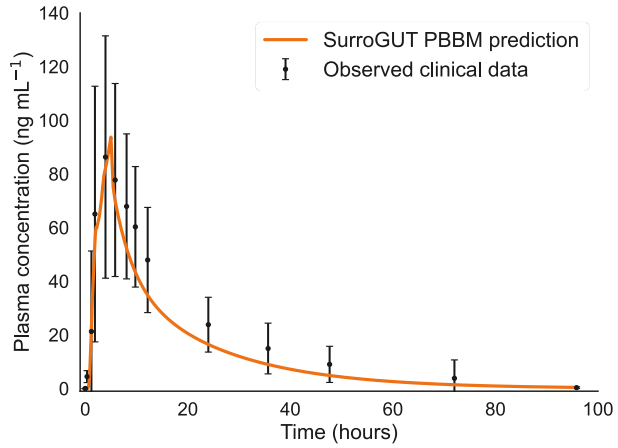
Distribution Metabolism Excretion

Pharmacokinetic modeling

- PBPK/PBBM
  - With or without TIM data
- IVIVC

GP

4 Outcome



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Advanced stomach and small intestine model

Physiologically relevant simulation of the upper GI tract

Tiny-TIM*sg*

Watch here

- Dynamic secretion of GI fluids
- Peristaltic motility
- *In situ* digestion of real food
- Gastric emptying & pH profile
- Absorption of drug-saturated media

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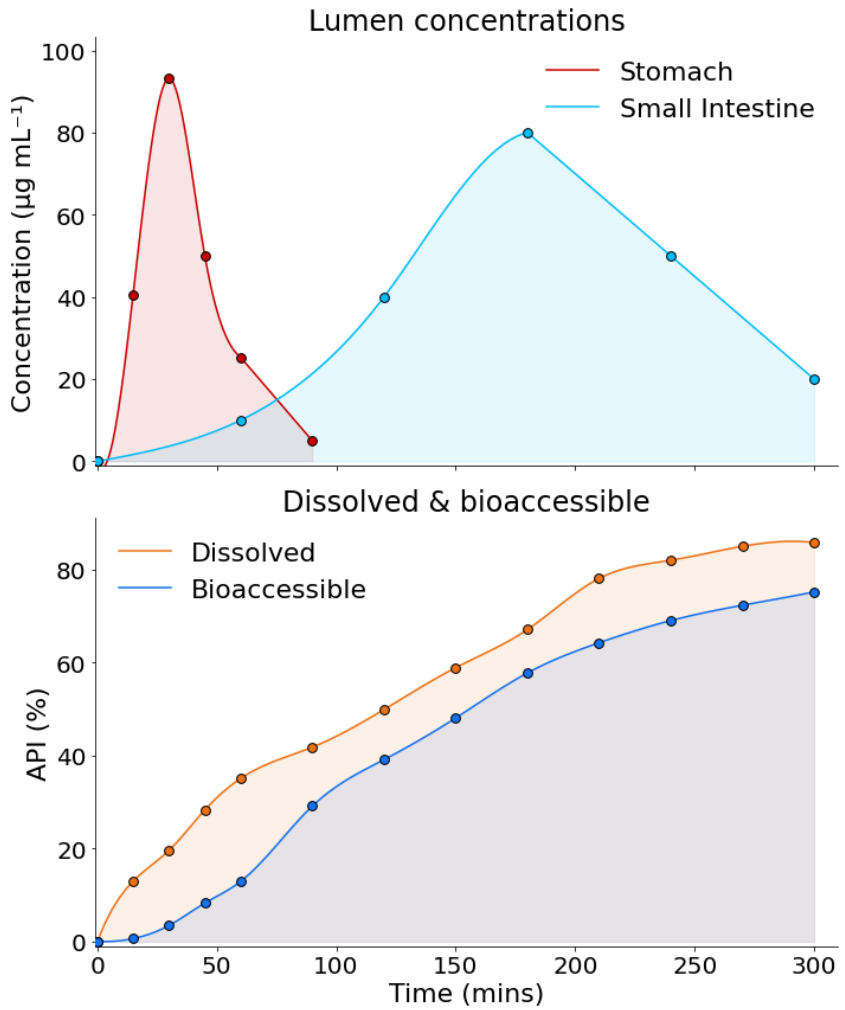
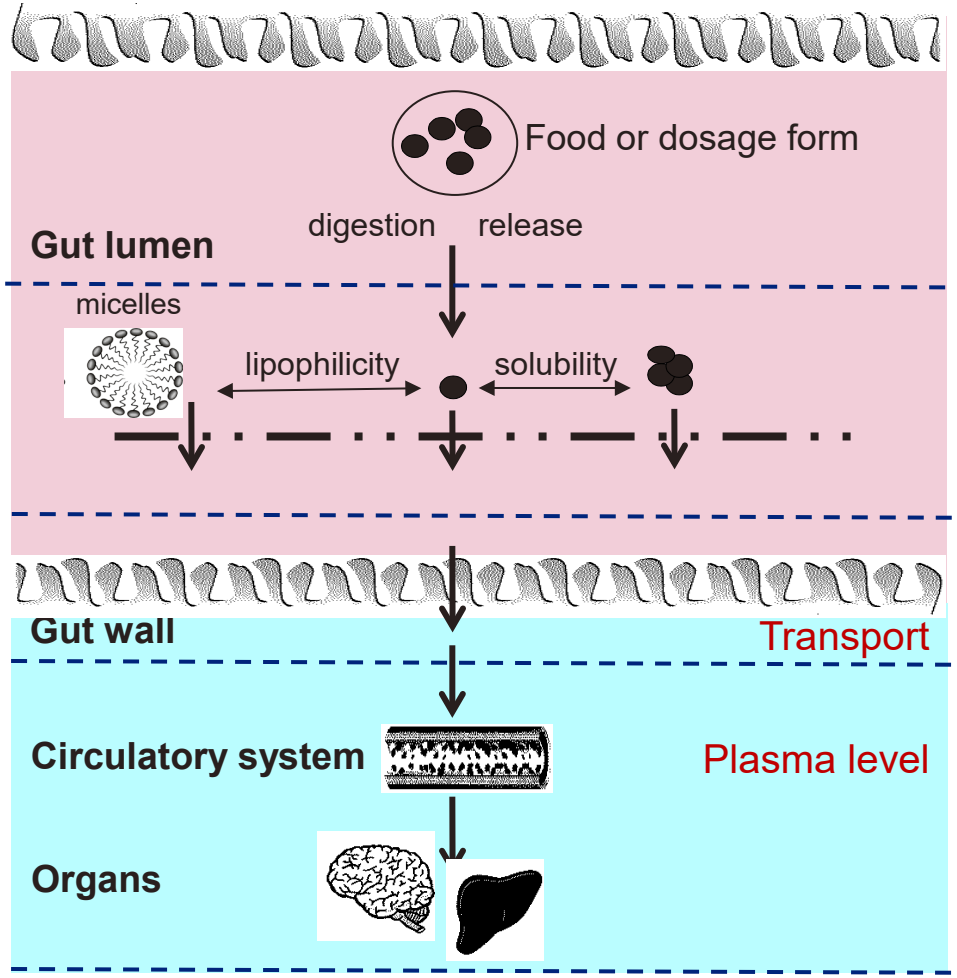
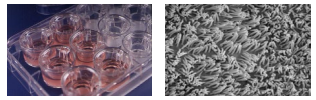
TIM allows for bioaccessibility assessment



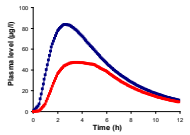


TIM

Intestinal cells



PBPK modeling



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TIM Applications

Extensive experience across pharma and food research

Formulation Comparisons & Bioequivalence

(Schilderink et al; 2020)

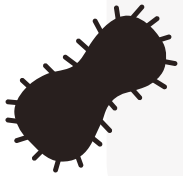
PPI, ARA, Food Effect & Drug-Drug Interaction

(Lui et al 2021;2024, Piscitelli *et al.*,2023)

Disease & Age Group Modeling

Chronic pancreatitis

(Effinger *et al., 2021)*



Microbiome & Survival Studies

(with or without mucus)

Digestibility & Protein Quality

(Chiang *et al.*, 2022)

Case studies

TIM supports development of novel pediatric formulations (I)

Predictive power for pediatric patients

Aim:

- Validation of the predictive quality of tiny-TIM*sg* for three age groups (neonates, infant & toddlers)

Test products:

- Paracetamol (syrup) with age-relevant food matrices in tiny-TIM*sg*

Age groups (maturation, food matrice):

- Neonates: 0-1 month; 3.6 kg; formula milk
- Infants: 1-6 months; 5.9 kg; formula milk, mixed fruit sauce
- Toddlers: 6–24 months; 10kg; milk+cereals, juice+cookie

Parameters	Neonate	Infant	Toddler
Gastric volume	107 mL	148 mL	172 mL
Meal 0/3h	90/90 mL	125/50 mL	142/94 mL
Gastric emptying	$T_{1/2}$ = 60 min	$T_{1/2}$ = 60 min	$T_{1/2}$ = 70 min
Gastric pH 0 – 3h	6.7 → 4.0	6.7 → 3.2	6.7 → 2.4
Gastric pH 3 – 6h	6.7 → 4.0	3.8 → 3.2	3.7 → 2.4
Intestinal secretions 0 – 3h	50%	75%	100%
Intestinal secretions 3 – 6h	50%	50%	50%

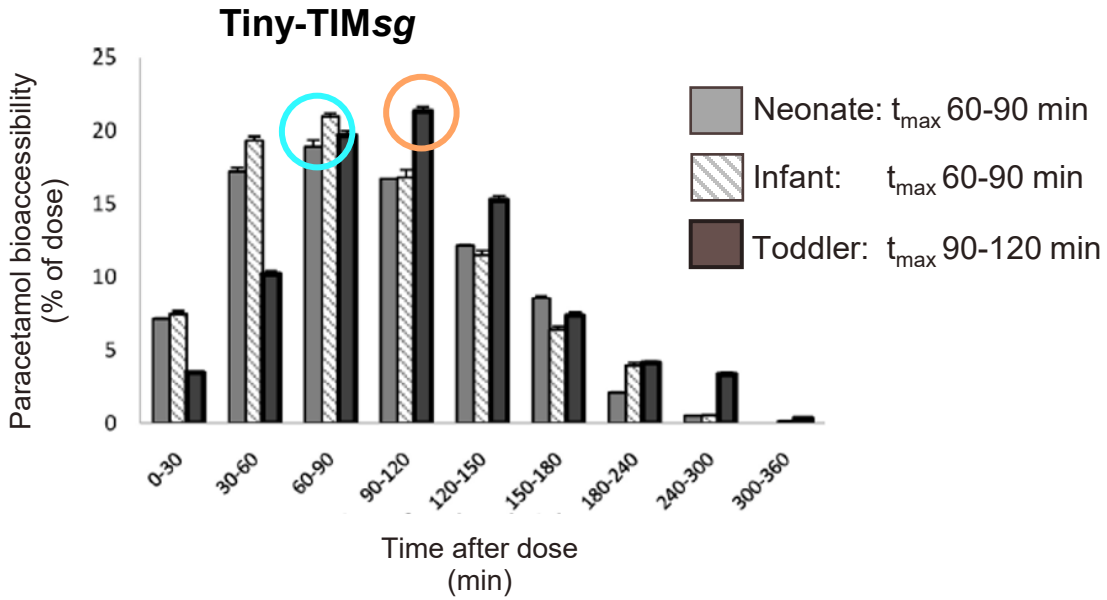
Havenaar et al. Int J Pharm 2013

TIM supports development of novel pediatric formulations (II)

Predictive power for pediatric patients

Results:

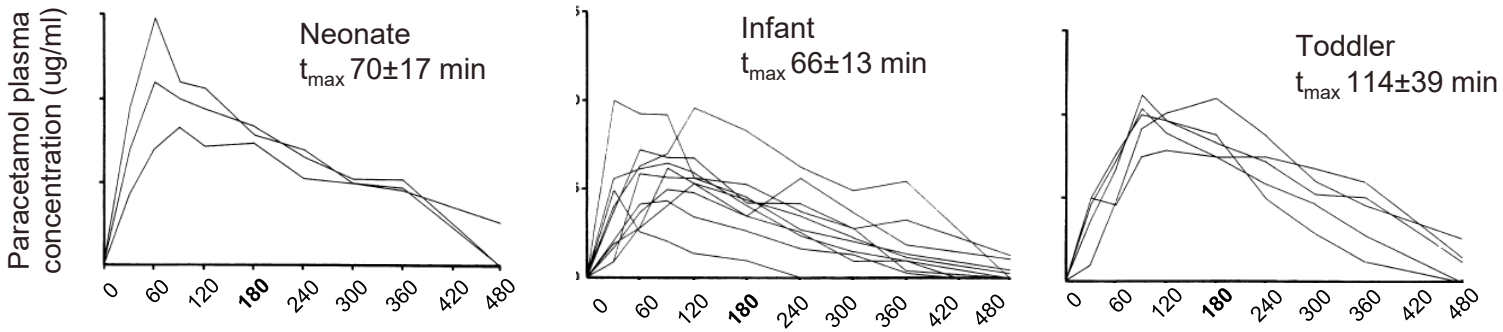
- Total bioaccessibility (BA) ~85% for all age groups
- T_{max} of toddler was delayed compared to younger children
- BA was in line with clinical pediatric plasma concentration curves



Conclusion:

- Validation showed the potential predictive quality of the tiny-TIM*sg* for three pediatric age groups

In vivo



Havenaar et al. Int J Pharm 2013; Comparison to Hopkins et al. 1990

Co-administration of oral drugs with acid-reducing agent (I)

TIM predictions matched *in vivo* performance

Aim:

- Predict effect of co-administration of drugs with acid-reducing (ARA) on oral absorption

Test products:

- 12 compounds: mostly basic, several salt forms

Test conditions:

- Fasted: Glass of water with gastric juice, pH 3.0
  Secretion of HCl dropped pH to 1.5 in 30mins
- Fasted ARA: Glass of water, neutral pH
  No simulated secretion of HCl

Drug	pKa	Form	ARA effect
Dasatinib	6.8	Free base	Negative[29]
Dipyridamole	6.2	Free base	Negative[29]
GDC-A	3.19	Free base	No
GDC-B	2.8, 5.4	Free base	Negative
GDC-C	3.7, 5	Free base	Negative
GDC-E	8.55	Free base	No
GDC-F	3.1, 4.8	Free base	No
Alectinib	7.1	HCL Salt	No[33]
Atazanavir	4.3	Sulfate Salt	Negative[32]
Erlotinib	5.6	HCL Salt	Negative[29]
GDC-D	8.6	Dimesylate Salt	Negative
Ketoconazole	2.9, 6.5	Free base	Negative[29]

 Liu et al., J Pharm.Sci, 2021

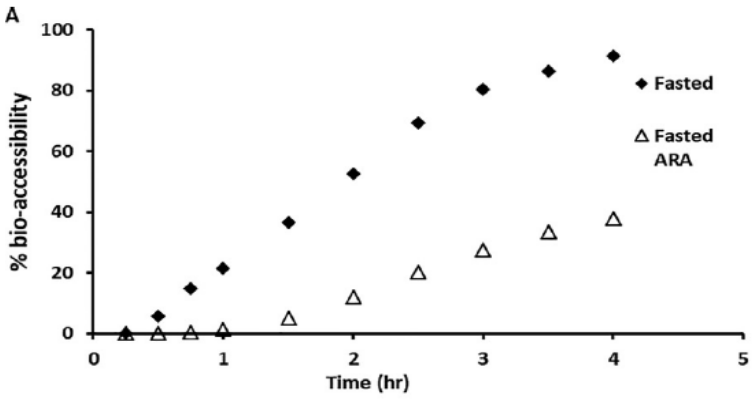
Co-administration of oral drugs with acid-reducing agent (II)

TIM predictions matched *in vivo* performance

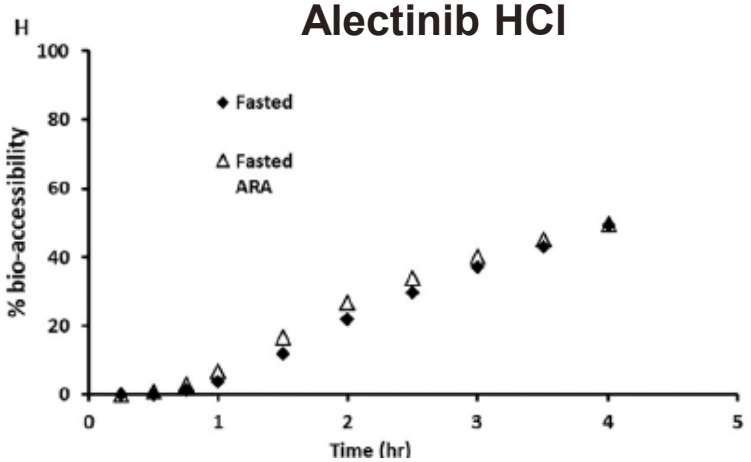
Results:

Ratio ARA/Non-ARA	Dasatinib	Alectinib HCl	Atazanavir sulfate
Tiny-TIMsg bioaccessibility	0.4	1	0.7
Clinical studies AUC	0.4	1	0.06 – 0.41

Dasatinib

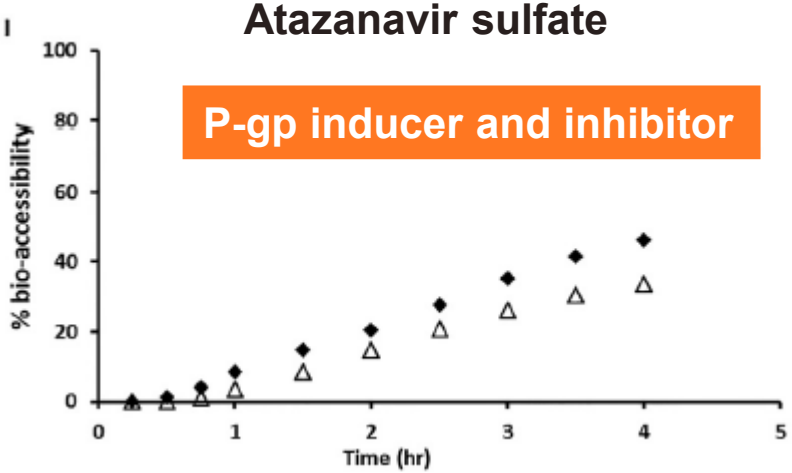


Alectinib HCl



Atazanavir sulfate

P-gp inducer and inhibitor



 Liu et al., J Pharm.Sci, 2021

Genentech InnoGI technologies

Co-administration of oral drugs with acid-reducing agent (III)

TIM predictions matched *in vivo* performance

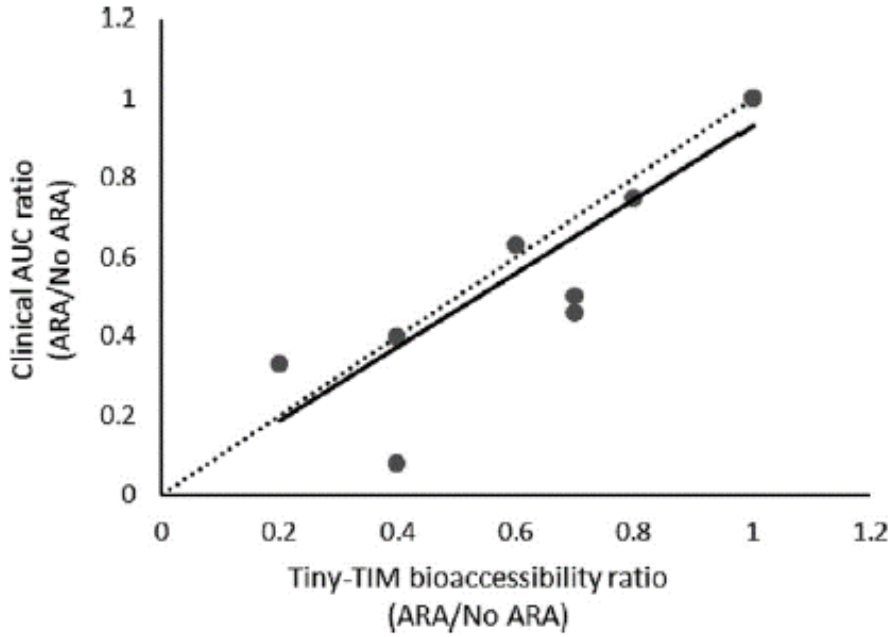
Results (cont.):

- 8/12 drugs showed high* predictivity, 4/12 moderate** predictivity
- Transporters and intestinal metabolism contribute to difference between BA and AUC ratio

Conclusion:

Tiny-TIM*sg*

- successfully predicted the effect of co-dosing ARA on oral absorption qualitatively and quantitatively.
- is a very reliable GI model for predicting ARA effect



Liu et al., J Pharm.Sci, 2021

* difference experimental ratio is < 0.2
** difference experimental ratio is > 0.2

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Food effect assessment in tiny-TIM*sg* (I)

Successful prediction for 20 drugs across all BCS classes

Aim:

- Assess the ability of tiny-TIM*sg* to predict the effect of food on the absorption of oral drugs

Test products:

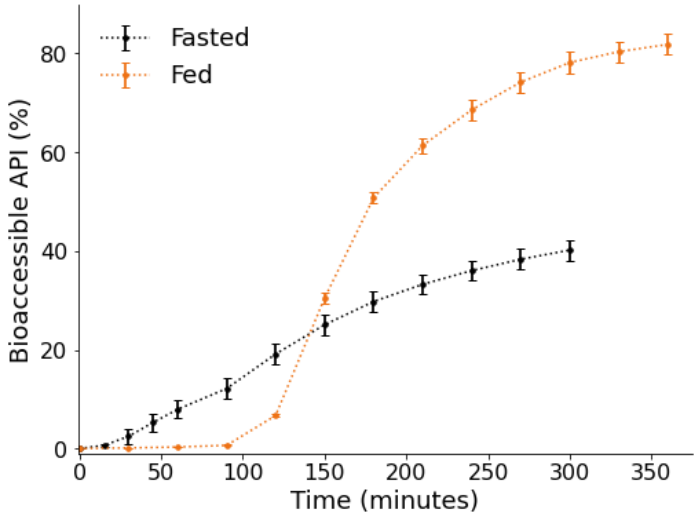
- 20 compounds covering all BCS classes
- Neutral, acidic, salt of acid, basic, and salt of basic drugs
- Different formulations

Test conditions:

- Fasted state: glass of water
- High fat meal
- Low fat meal

Food ingestion can change

- Intragastric pH
- Gastric transit time
- Secretion digestive enzymes
- Bile secretion
- Motility
- Viscosity



 Liu et al., J Pharm.Sci, 2024

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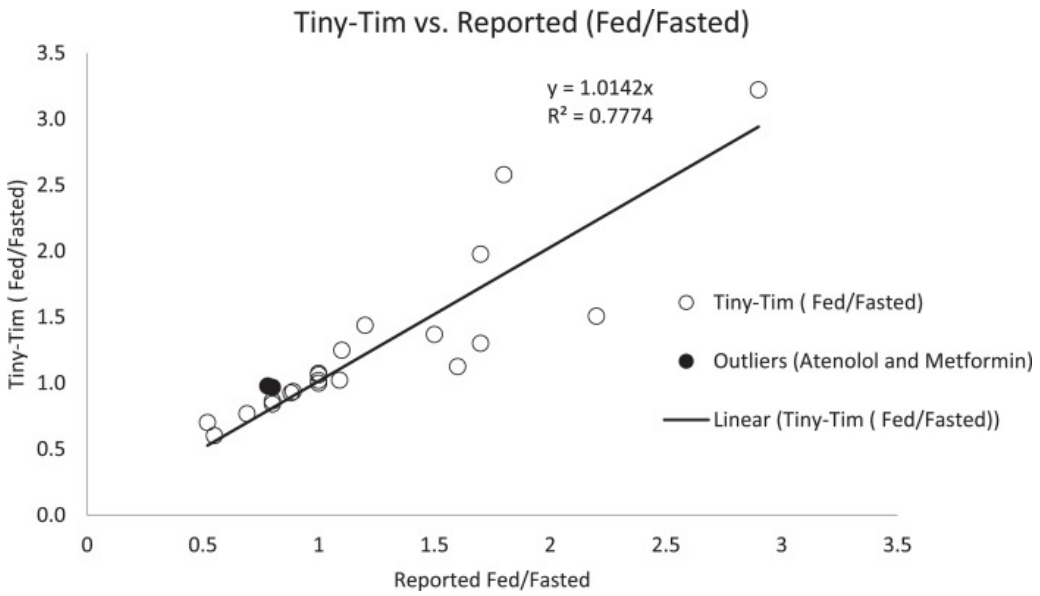
Food effect assessment in tiny-TIM*sg* (II)

Successful prediction for 20 drugs across all BCS classes



Results:

Tiny-TIM*sg*

- predicted food effect ratios were in good agreement with the reported data in humans
- predicted no food effect for atenolol and metformin

Conclusion:

- Tiny-TIM*sg* can successfully capture the effect of food on oral absorption that is related to the physicochemical properties of the drug.

 Liu et al., J Pharm.Sci, 2024

Genentech
A Member of the Roche Group

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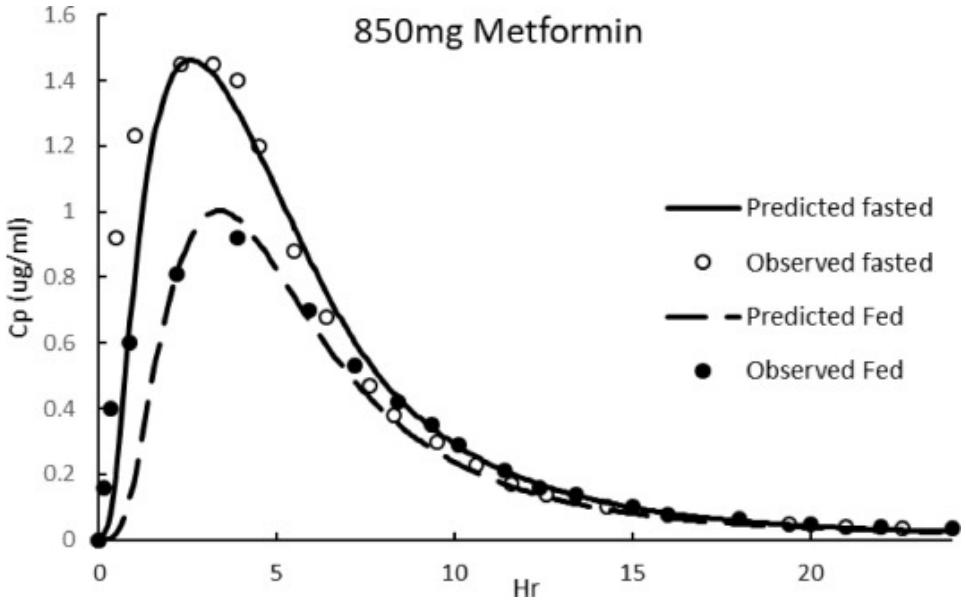
Food effect assessment in tiny-TIM*sg* (III)

Using tiny-TIM*sg* dissolution data as modeling input

Modeling for metformin

- Metformin (BCS Class III) *in vivo* absorption involves multiple transporters.
- Tiny-TIM*sg* dissolution data for metformin were imported into GastroPlus®.
- Strong prediction of human PK profile and negative food effect (C_{max} and T_{max} in agreement with *in vivo* data).



 Liu et al., J Pharm.Sci, 2024

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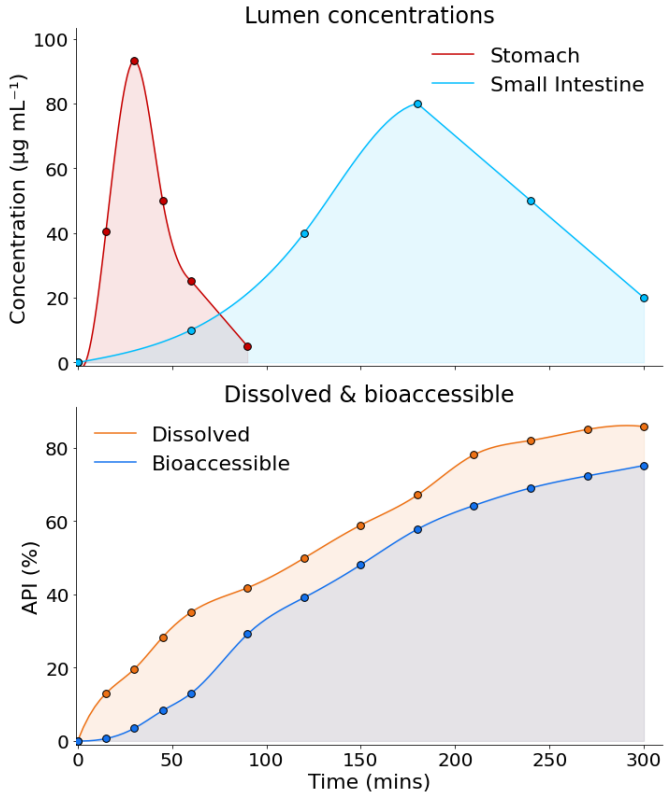
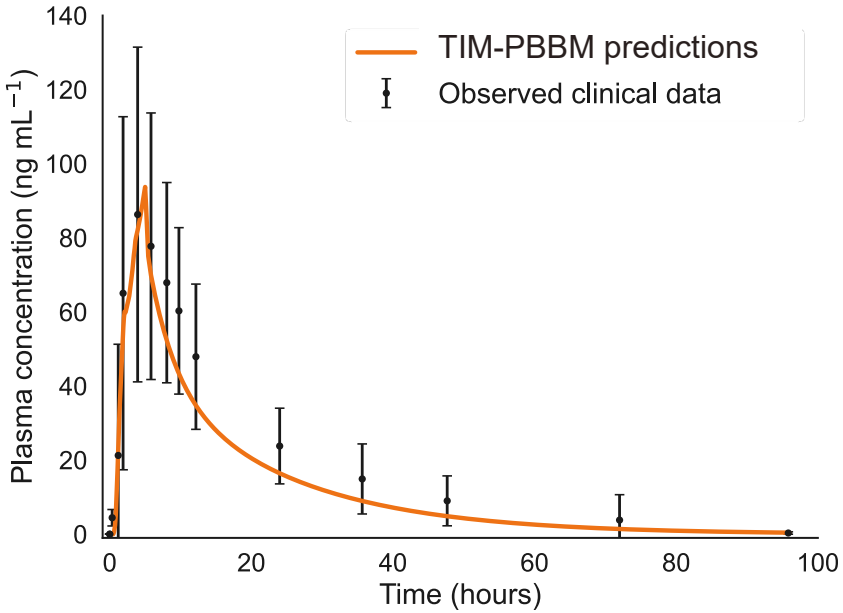
TIM-PBBM

TIM provides predictive input for PBBM

Predicting *in vivo* behavior of MR formulations

- Build & validate PBPK model
- Perform TIM experiments as most physiologically relevant *in vitro* dissolution
- Convert luminal and BA data into TIM dissolution profile
- Predict PK profile
- Assess bioequivalence



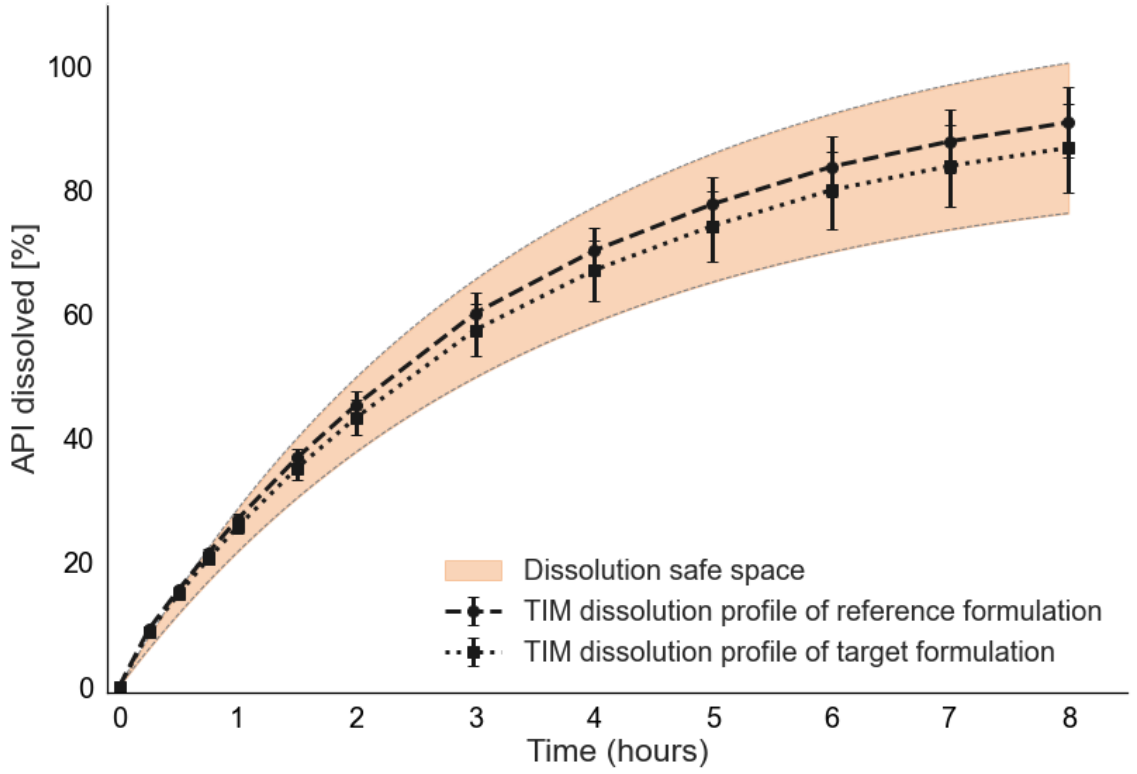


TIM-PBBM to support virtual bioequivalence testing

TIM dissolution safe space for complex formulations

TIM biopredictive dissolution testing at extremes of physiological and formulation parameter space

- pH range (incl. ARAs)
- Motility / hydrodynamics
- Gastric emptying rate
- Dose volume (mL drink)
- Meal type (fed state)



Grant 1U01FD007959-01 PI Dr Jie Shen Northeastern University

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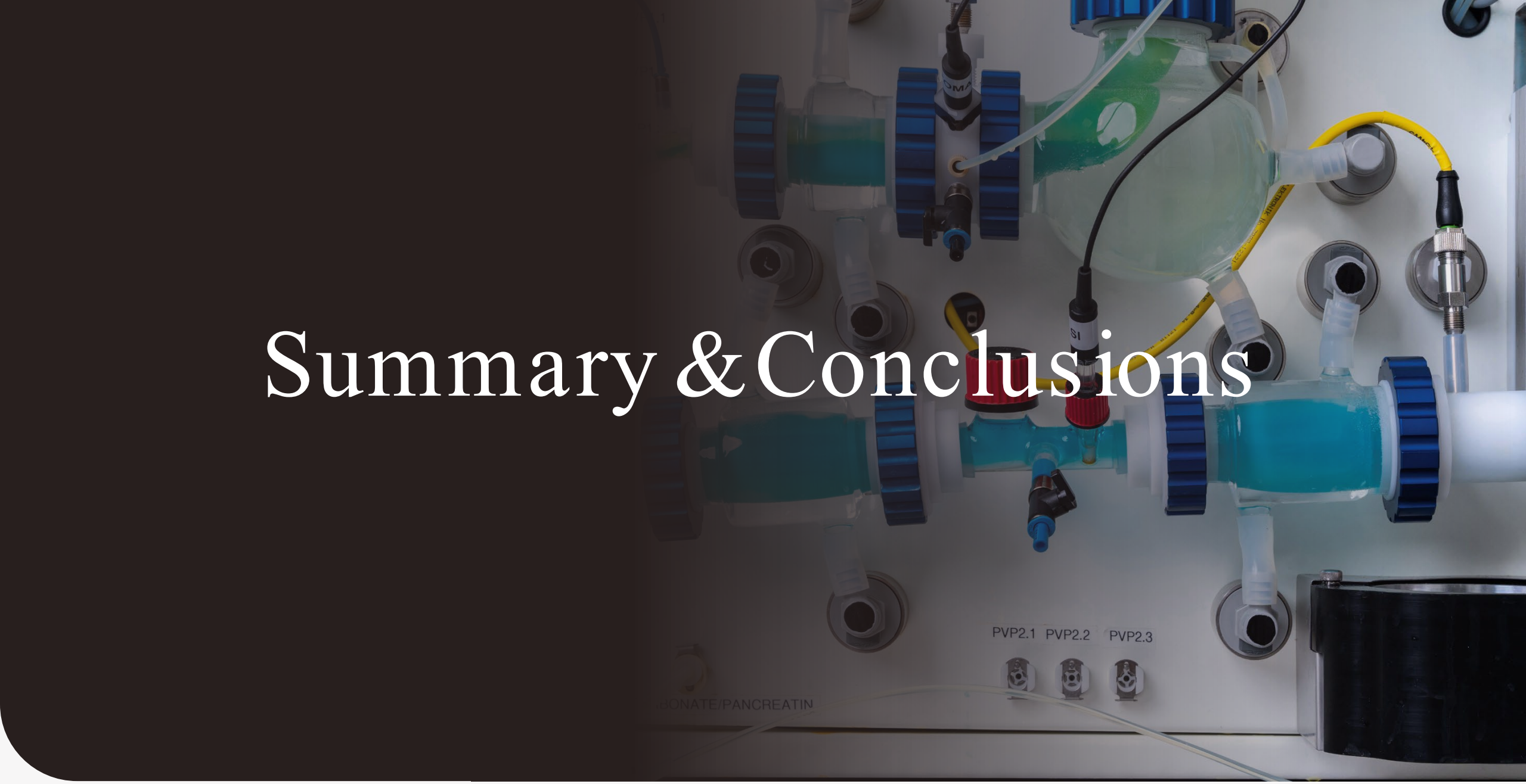
Summary & Conclusions



Summary

One tool, multiple solutions

The TIM Technology platform

- Closely mimics the full dynamic, physical and biochemical complexity of the GI tract
- Provides strong predictions of luminal conditions and human bioavailability, also in combination with food, PPI or for specific (age) populations

Tiny-TIM*sg* proven to be

- Physiologically-relevant tool for testing complex formulations and poorly soluble API
- Able to establish BE between different strengths and dosage forms
- Improve PBPK/PBBM predictions using high quality TIM data

Concluding Remarks

Considerations

- Define critical parameters for additional strengths of MR products Grant 1U01FD007959-01 PI Dr Jie Shen Northeastern University
- TIM studies could replace clinical BE studies in certain circumstances
  - e.g. BCS-based biowaivers; SUPAC; food effect, PPI & pediatric biowaivers; locally-acting API
  - Guidance requested to harmonize use of advanced dissolution methods for these cases
- Added value of including the TIM-2 colon model for evaluation of MR formulations

Thank you for your attention!

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