Cancer-Driven Changes in Small Intestinal & Colonic Drug-Metabolising Enzymes and Transporters: Updating Cancer Populations for PBPK Modelling and PK Implications

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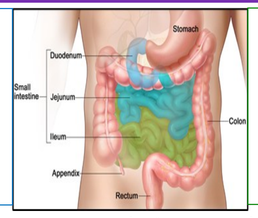
Background / Objectives

Small intestine cancer is rare, with a steady rise over the last decades. Because of its rarity, clinical trials are limited. On the other hand, **colorectal cancer** is the third most common type of cancer, with half of patients having liver metastasis. Cancer is not a unique disease and clinical trials in oncology initially recruit heterogeneous populations, without covering all types of variability. The population may not be representative, leading to variability in PK. Physiologically-based pharmacokinetic (PBPK) models can be used as an alternative to clinical studies for dosing guidance. These models require cancer-specific systems parameters for each type of cancer, which are scarce. Example of such parameters is the abundance of drug-metabolising enzymes (DMEs) and transporters [1]. Despite the important role of the gastrointestinal tract (GIT) in the PK of drugs, the abundance of PK proteins and their alterations in GIT tumours have not been studied. Therefore, this study aimed to:

- investigate, for first time, the impact of **small intestine** and **colon cancer** on the abundance of **DMEs and transporters**, by comparing protein levels in healthy controls vs non-tumour adjacent to tumour vs tumour tissues,
- use the experimental data from the current study, in addition to other cancer-specific parameters previously defined [2,3,4], to **create sub-populations for small intestine and colon cancer** in Simcyp,
- assess potential **implications for PK** of non-anticancer and anticancer drugs in patients with GIT cancer.

Methods

- 5 Healthy Small Intestine Samples
- 7 Non-tumour Small Intestine Samples
- 8 Tumour Small Intestine Samples



- 5 Healthy Colon Samples
- 2 Non-tumour Colon Samples
- 3 Tumour Colon Samples

Epithelial cells extraction, tissue homogenisation → Pool each group of samples → Protein digestion → LC-MS/MS → MQ → Abundance of PK proteins → Simcyp Version 23 Release 1

Small Intestine
- 4 populations developed
- simulations on 68 substrates

Colon
- 6 populations developed
- simulations on budesonide (controlled-release formulation)

Table 1. Small intestine cancer populations used/developed for PBPK simulations in Simcyp.

Population	Assumption/Definition	Systems parameters
Healthy	Default **Healthy** volunteers population in Simcyp	Based on Healthy volunteers population
Cancer-D	Default **Cancer** population in Simcyp	Differences from Healthy volunteers: age-sex distribution, weight-height relationship, ↑α-1 acid glycoprotein, ↓albumin & haematocrit, ↓renal function, changes in some liver transporters
ASIN Cancer	**A**ll **S**mall **I**ntestine **N**on-tumour (but not healthy)	Same as Cancer-D + abundance of CYPs, UGTs, transporters in non-tumour SI samples from SI cancer patients
ASIC Cancer	**A**ll **S**mall **I**ntestine **C**ancerous	Same as Cancer-D + abundance of CYPs, UGTs, transporters in tumour SI samples from SI cancer patients
ALN, ASIN Cancer	**A**ll **L**iver **N**on-tumour (but not healthy) and **ASIN**	Same as ASIN Cancer + abundance of DMEs, transporters & MPPGL[1] values in the liver (non-tumour part) of patients with CRLM[2,*]
ALN, ASIC Cancer	**A**ll **L**iver **N**on-tumour (but not healthy) and **ASIC**	Same as ASIC Cancer + abundance of DMEs, transporters & MPPGL values in the liver (non-tumour part) of patients with CRLM[*]

Table 2. Colon cancer populations used/developed for PBPK simulations in Simcyp[**].

Population	Assumption/Definition	Systems parameters
Healthy	Default **Healthy** volunteers population in Simcyp	Based on Healthy volunteers population in SimCYP
Cancer-D	Default **Cancer** population in Simcyp	Based on Cancer patients in SimCYP
ACN Cancer	**A**ll **C**olon **N**on-tumour (but not healthy)	Same as Cancer-D + abundance of CYP3A4 and CYP3A5 in non-tumour Colon samples from Colon cancer patients
ACC Cancer	**A**ll **C**olon **C**ancerous	Same as Cancer-D + abundance of CYP3A4 and CYP3A5 in tumour Colon samples from Colon cancer patients
ALN, ACN Cancer	**A**ll **L**iver **N**on-tumour (but not healthy) and **ACN**	Same as ACN Cancer + abundance of DMEs, transporters & MPPGL[1] values in the liver (non-tumour part) of patients with CRLM[2,*]
ALN, ACC Cancer	**A**ll **L**iver **N**on-tumour (but not healthy) and **ACC**	Same as ACC Cancer + abundance of DMEs, transporters and MPPGL values in the liver (non-tumour part) of patients with CRLM[*]
ALC, ACN Cancer	**A**ll **L**iver **C**ancerous and **ACN**	Same as ACN Cancer + abundance of DMEs, transporters & MPPGL values in the liver (tumour part) of patients with CRLM[*]
ALC, ACC Cancer	**A**ll **L**iver **C**ancerous and **ACC**	Same as ACC Cancer + abundance of DMEs, transporters & MPPGL values in the liver (tumour part) of patients with CRLM[*]

[1]Microsomal Protein Per Gram of Liver, [2]Colorectal Cancer with Liver Metastasis

*ALN & ALC Populations & the incorporated values were gradually generated by Vasilogianni et al., 2021, DMD; Vasilogianni et al, 2021, BJCP; Vasilogianni et al, 2022, CPT.

**Simulations were performed for budesonide. The compound file for budesonide (controlled-release formulation) was previously developed by Han et al, 2023, Pharmaceutics [5].

Results

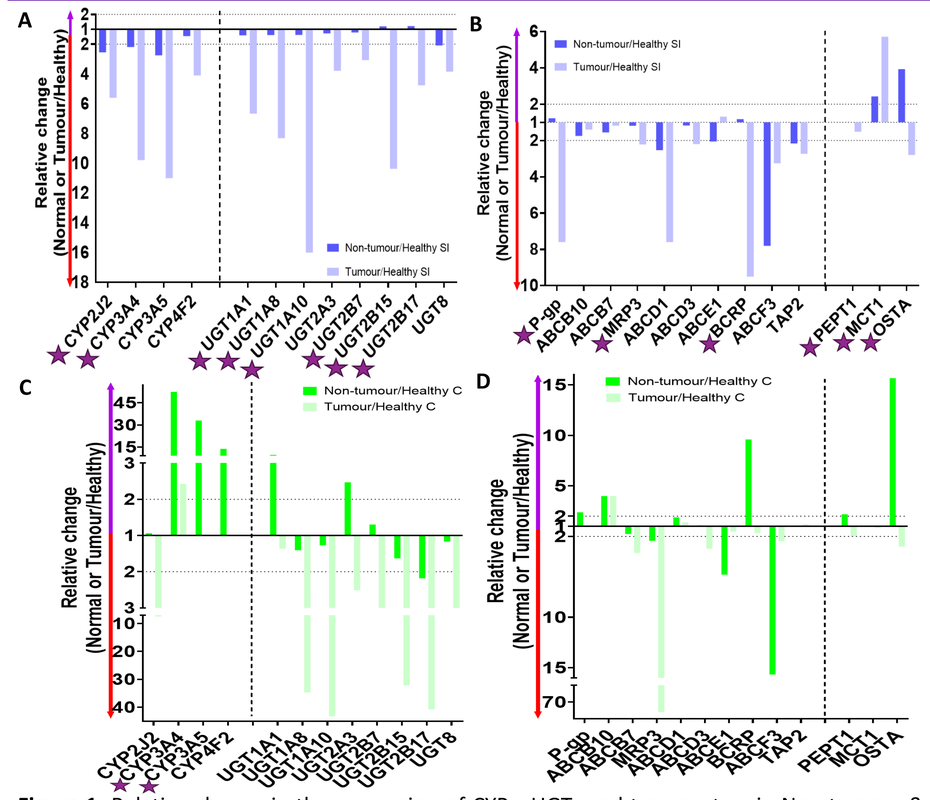
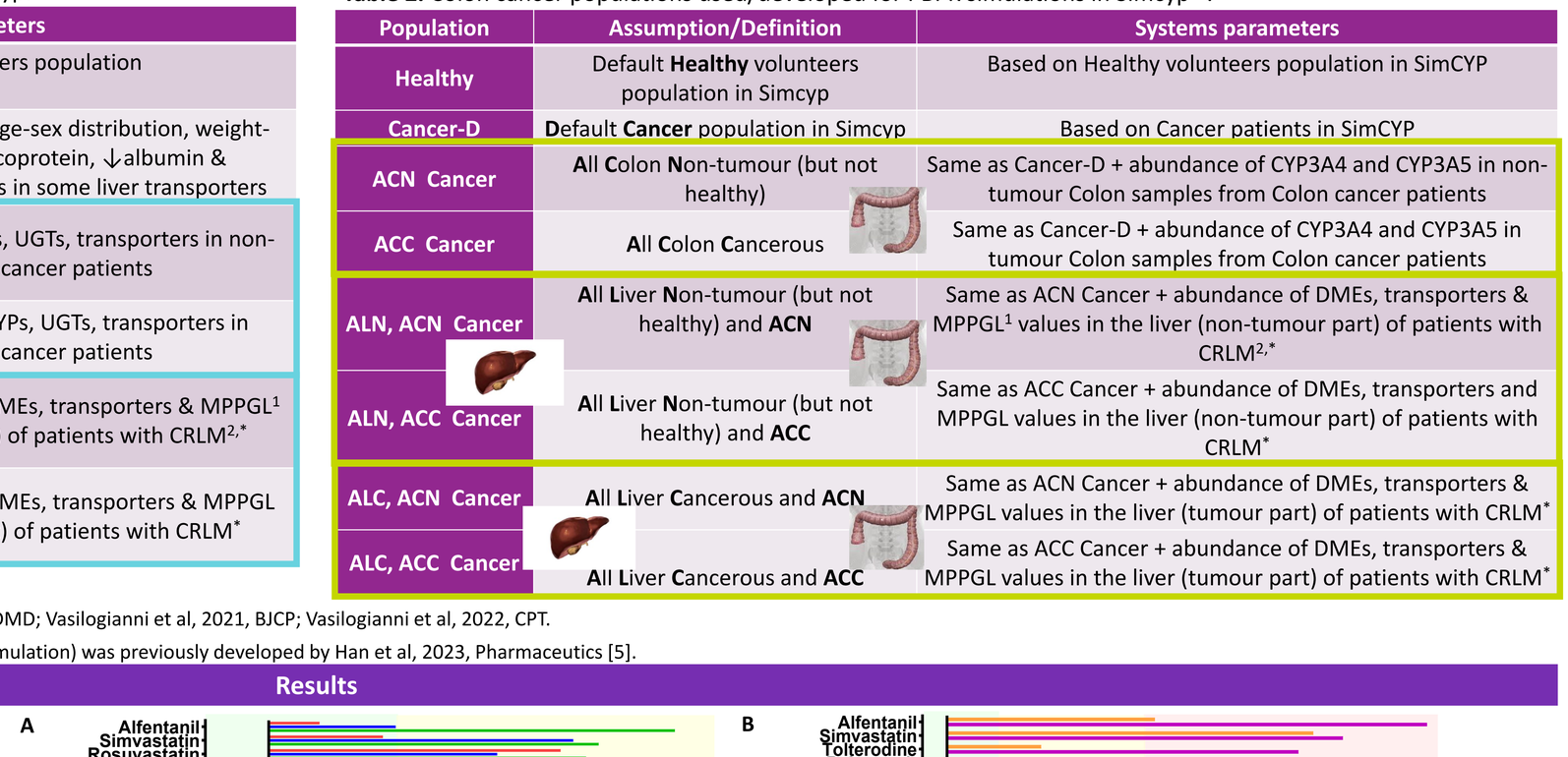


Figure 1. Relative change in the expression of CYPs, UGTs and transporters in Non-tumour & Tumour compared with Healthy Small Intestine (SI) and Colon (C). The red arrow shows decrease compared with Healthy, and the purple arrow increase. The asterisks mark proteins for which changes in abundance were incorporated into Simcyp.



	Rel. CL	E_H	F_G	f_u, binding protein	Elimination
Alfentanil	2.0	0.3	0.5	0.1, AGP	CYP3A4
Ibrutinib	2.2	0.9	0.3	0.03, HSA	CYP3A4
Rosuvastatin	2.8	0.02	1.0	0.11, HSA	Renal
Simvastatin	3.4	0.7	0.02	0.02, HSA	CYP3A4

	Rel. CL	E_H	F_G	f_u, binding protein	Elimination
Docetaxel	2.0	0.9	0.001	HSA, AGP	CYP3A4
Dexamethasone	2.1	0.2	1.0	0.24, HSA	CYP3A4
Oxycodone	2.1	0.4	0.9	0.58, HSA	CYP3A4/2D6
Itraconazole	2.4	0.7	0.9	0.02, HSA	CYP3A4
Bufuralol	2.5	0.5	1.0	0.19, HSA	CYP2D6
Atomoxetine	2.6	0.4	0.9	0.02, HSA	CYP2D6
Metoprolol	2.7	0.5	1.0	0.88, HSA	CYP2D6
Nebivolol	2.8	0.9	0.8	0.02, HSA	CYP2D6
Rosuvastatin	2.9	0.02	1.0	0.11, HSA	Renal
Tolterodine	2.9	0.7	1.0	0.04, AGP	CYP2D6
Dextromethorphan	3.1	0.9	0.8	0.50, HSA	CYP2D6
Triazolam	3.1	0.2	0.7	0.18, HSA	CYP3A4
Cyclosporine	3.4	0.2	0.6	0.04, HSA	CYP3A4
Sildenafil	3.9	0.4	0.6	0.04, HSA	CYP3A4
Nifedipine	4.2	0.4	0.7	0.04, HSA	CYP3A4
Midazolam	4.2	0.4	0.6	0.03, HSA	CYP3A4
Alfentanil	5.2	0.3	0.5	0.1, AGP	CYP3A4
Ibrutinib	5.7	0.9	0.3	0.03, HSA	CYP3A4
Raltegravir	6.5	0.4	0.6	0.17, HSA	UGT1A1
Simvastatin	8.4	0.7	0.02	0.02, HSA	CYP3A4

Figure 2. Relative clearance (CL) of drugs in different populations. Relative CL in Healthy and Cancer-D to ASIC Cancer, and ASIN Cancer to ASIC Cancer population (**A**), and Healthy and Cancer-D to ALN, ASIC Cancer population (**B**). The light green rectangle shows the drugs with < 2-fold change in CL, and the amber and the red > 2- and 5-fold higher CL, respectively. The tables show the relative CL of drugs with different properties, based on relative CL in Cancer-D/ASIC (**A**), and Cancer-D/ALN, ASIC Cancer (**B**). The values for the several drug properties are based on the Healthy volunteers. E_H: Hepatic extraction ratio; F_G: Fraction of substrate escaping gut metabolism (1 - the gut Ext. Ratio); f_u: fraction unbound, HSA: human serum albumin; AGP: alpha-1-acid glycoprotein.

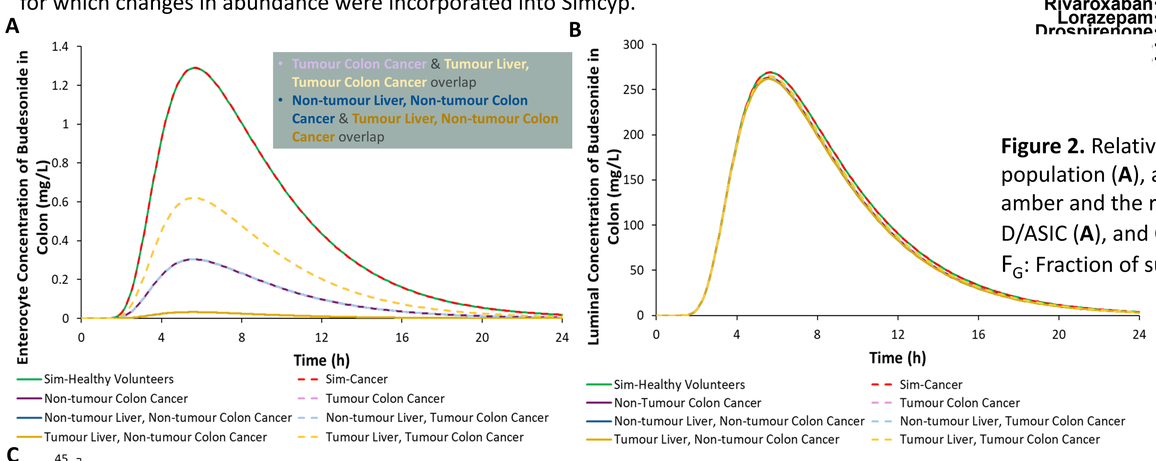


Figure 3. Mean predicted enterocyte (**A**), luminal (**B**) and systemic concentration (**C**) over time (24 hours) after oral administration of budesonide, in different populations.

Table 3. Area under the curve (AUC) and F_{gM} of budesonide in different populations.

Population	AUC (nM·h)	F_{gM}*
Sim-Healthy Volunteers	31.7	0.29
Sim-Cancer	38.9	0.28
Non-Tumour Colon Cancer	25.5	0.18
Tumour Colon Cancer	29.7	0.21
Non-Tumour Liver, Non-Tumour Colon Cancer	62.9	0.16
Non-Tumour Liver, Tumour Colon Cancer	85.3	0.21
Tumour Liver, Non-Tumour Colon Cancer	422.8	0.15
Tumour Liver, Tumour Colon Cancer	558.5	0.20

*fraction of drug escaping gut metabolism when the M-ADAM model is selected and considers drug accessing the enterocyte via both apical (first-pass) and basolateral (potentially systemic) membrane

Conclusions

- **Cancer-driven changes in drug metabolism and transport** were observed in small intestine and colon cancer.
- Altered abundance of ADME proteins, in addition to changes in other system parameters, **could impact the PK** of drugs dosed orally in these patients.
- The **importance of the incorporation of population-specific abundance of PK proteins in PBPK models** for the prediction of PK is highlighted.
- The values reported here should enable **updating systems parameters** within existing PBPK platforms in relation to abundance of DMEs and transporters **to reflect biological values**. Verification with observed clinical PK data creates the basis for what has been coined as "master files" to be used with different new drugs substrates.

References

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