Quantitative Systems Pharmacology Modeling Applications at Different Stages of Drug Development

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ASCPT Webinar Series (Early Career Community)

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Quantitative systems pharmacology (QSP) modeling can be applied at different stages of drug development, from early research to late stage development

- Case studies:
  - **Preclinical:** Mechanistic insights for AZD3458, a novel selective PI3Kγ immuno-modulator
  - **Late-stage clinical development and translation between patient populations:** Quantitative systems pharmacology model of potassium homeostasis for Lokelma

Case 1: Mechanistic insights for AZD3458, a novel selective PI3Kγ immuno-modulator, using a quantitative systems model

Clinical Motivation

- In 2018, an estimated 1,735,350 new cases of cancer will be diagnosed in the United States and 609,640 people will die from the disease
- Cancer growth and progression are associated with immune suppression
- Monoclonal antibodies that target immune checkpoints provided an immense breakthrough in cancer therapy
- However, response rates remain relatively low; therefore, combination studies with small molecules, chemotherapy and other biologics are of interest to improve anti-tumor responses

Treatments:
- **Checkpoint inhibitors, *e.g.* anti PD-[L]1, CTLA-4**

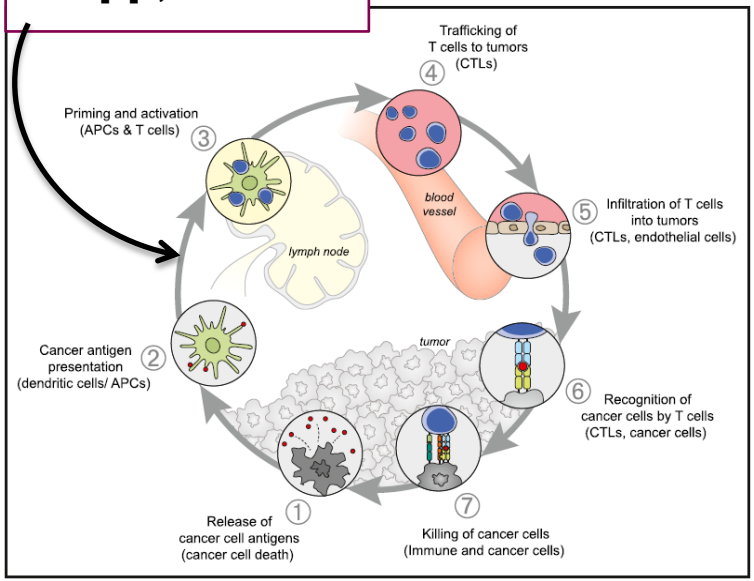
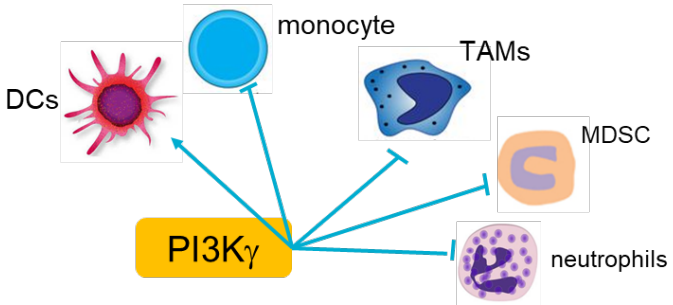


Figure 1. The Cancer-Immunity Cycle
The generation of immunity to cancer is a cyclic process that can be self propagating, leading to an accumulation of immune-stimulatory factors that in principle should amplify and broaden T cell responses. The cycle is also characterized by inhibitory factors that lead to immune regulatory feedback mechanisms, which can halt the development or limit the immunity. This cycle can be divided into seven major steps, starting with the release of antigens from the cancer cell and ending with the killing of cancer cells. Each step is described above, with the primary cell types involved and the anatomic location of the activity listed. Abbreviations are as follows: APCs, antigen presenting cells; CTLs, cytotoxic T lymphocytes.

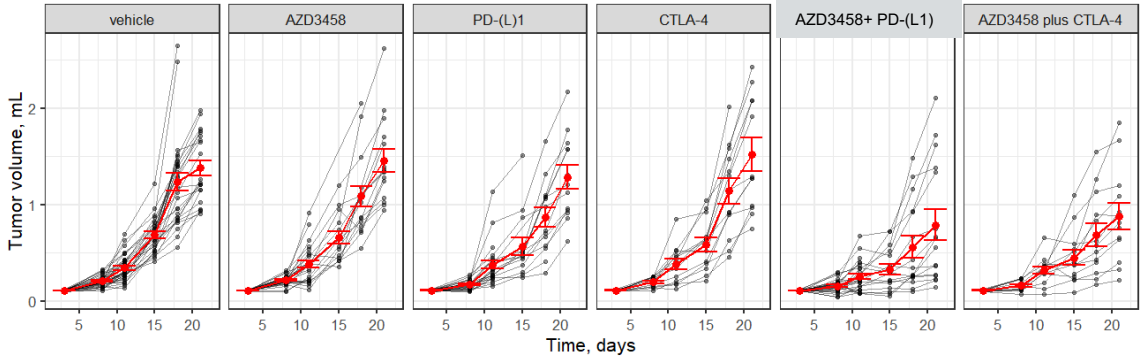
The PI3Kγ isoform is a key regulator of immune cell proliferation, survival, migration and activation

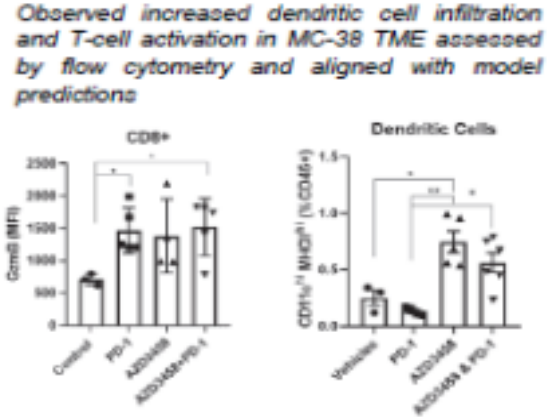
- **In the context of cancer, PI3Kγ inhibition may re-program myeloid cells, re-polarizes macrophages to an immuno-stimulatory state, and promote cytotoxic CD8 T cell activity, thereby eliciting a tumor immune response**
- **AZD3458 is a highly selective PI3Kγ clinical candidate with potential as monotherapy and in combination with checkpoint inhibition, to overcome resistance and to enhance efficacy of checkpoint inhibitors**



A QSP model was needed to understand the mechanism of action of AZD3458 (PI3Kɣ) and dose sequence optimization

- AZD3458 (PI3Kɣ) mono or anti-PD-(L1)/CLTA-4 is shown to have only limited efficacy in MC38. However, synergy is achieved with combination
- **Complex immune modulation: AZD3458(PI3Kɣ) was shown to increase CD8 and dendritic cells; however, the key contribution mechanism in anti-tumor response is not clear**
- **How dose sequencing affects anti-tumor responses is not clear**
- Could we use the model to identify responders vs. non-responders?





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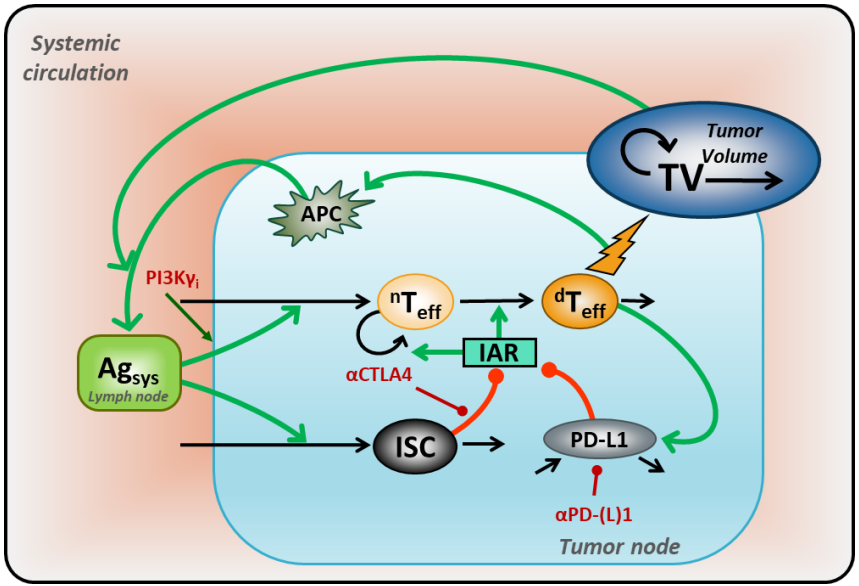
An immuno-oncology QSP model was adapted to incorporate PI3Kγ inh MoA in a MC38 syngeneic model

- **PI3Kγ :** $PI3K\gamma = k_{eff} \cdot \frac{1}{\left(1+\frac{Cc2}{K_{dAZD}}\right)}$;
  - $TN_{inf} = k_{Ln} \cdot \frac{Ag}{Ag+S_L} \cdot PI3K\gamma$
- **Infiltrated T cell proliferation and differentiation in TME:** $\frac{dT_{eff}^{n}}{dt} = \frac{kLn \cdot Ag_{sys}}{Ag_{sys}+sL} + k_{pro} \cdot T_{eff}^{n} \cdot IAR - k_{el} \cdot T_{eff}^{n} - k_{dif} \cdot IAR \cdot T_{eff}^{n}$; $\frac{dT_{eff}^{d}}{dt} = k_{dif} \cdot IAR \cdot T_{eff}^{n} - k_{apo} \cdot T_{eff}^{d}$
- **IAR (Immune activation rate function):** $IAR = (1 - PDL1_{free}) \cdot (1 - ISC^{*})$, **where** $ISC^{*} = \frac{Ag_{sys}}{Ag_{sys}+sR} \cdot \left(1 - I_{max,ctla4} \cdot CTLA4_{\ occ}\right)$
- Nonlinear mixed-effects (NLME) model analysis was performed. Parameter and relative standard error estimation were based on the stochastic approximation expectation maximization (SAEM) algorithm



PI3Kγ inh PK module (BID)

aPD-(L)-1 PK module (Q3D)

aCTLA4 PK module (Q3D)

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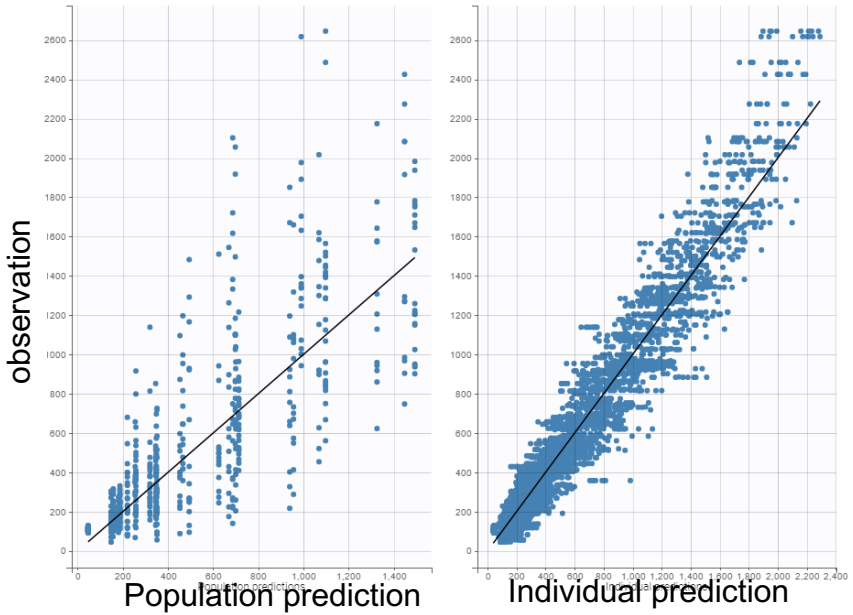
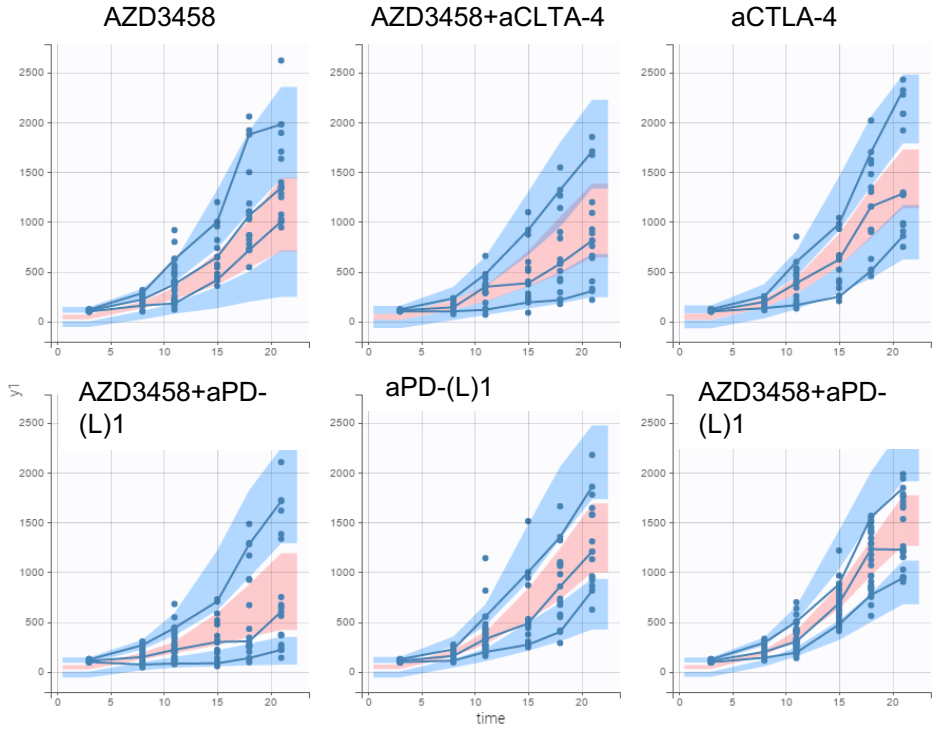
Model adequately described cohort- and individual-level tumor size dynamics patterns, for 4 compounds

anti-*PD-1, anti-PD-L1, anti-CTLA4, PI3Kγ inhibitor treatment regimens in MC38*





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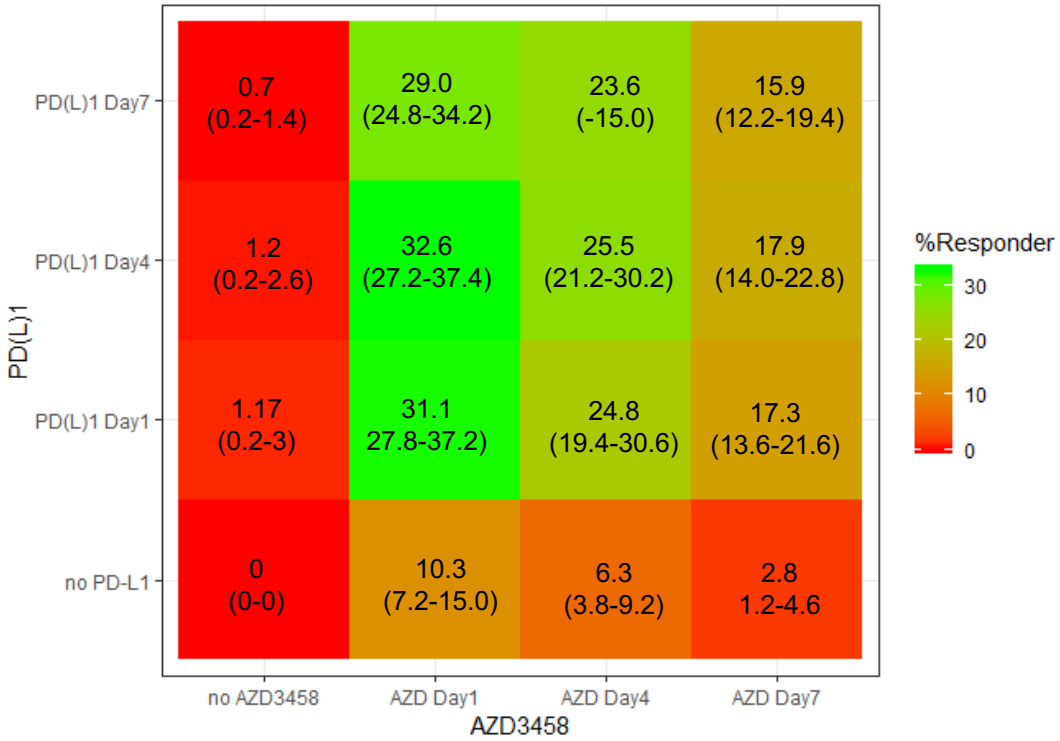
Application: Model suggests that dosing AZD3458 prior to anti-PD(L)1 leads to better efficacy

- A 50 trial-simulation of a virtual population (N=500) was used. Anti PD(L)-1 and AZD3458 were started either on days 1, 4 or 7 after animal inoculation
- Percentage of responders was calculated. Simulated percentage aligns well with observed data (e.g. ~30%)
- Simulations indicate that treating with AZD3458 prior to PD(L)-1 is preferred



L. Chu et al. *AACR American Association for Cancer Research, Atlanta, GA, March 29 – April 03, 2019*.

Summary

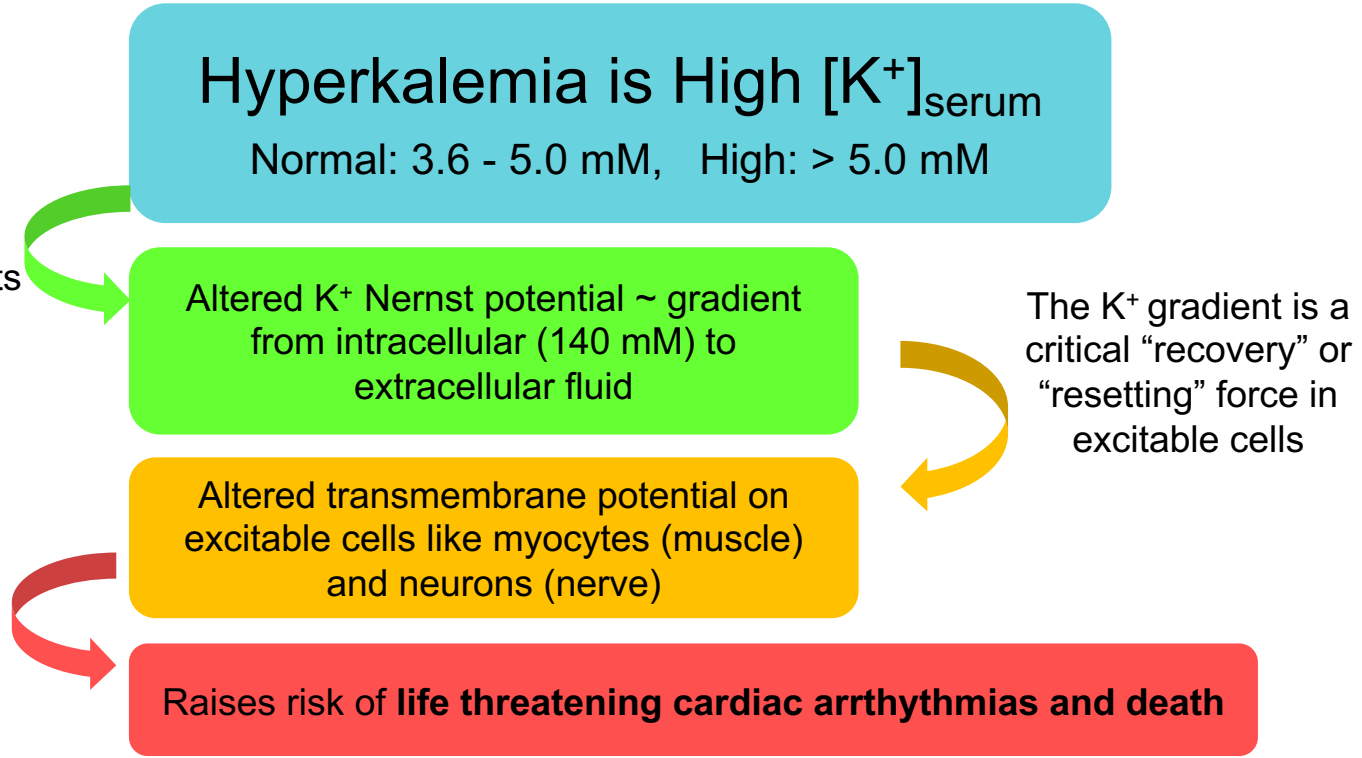
- **Utility of QSP in preclinical space for immuno-oncology**
  - Quantitative framing of target an biomarkers in disease and efficacy context
  - MoA elucidation
  - Understanding of responders vs. non-responders
  - Combination selection
  - Dose scheduling/sequencing
  - TME condition vs. response predictions
  - PKPD predictions
- **Soft skill development (communication with DMPK modelers, *in vivo* pharmacologist, cell biologist)**
- **Impact: Provide rationale for dose sequencing in combination study for team**

Case 2: Quantitative Systems Pharmacology Model of Potassium Homeostasis for Sodium Zirconium Cyclosilicate (SZC, LOKELMA®)

Hyperkalemia – What is it? Why is it bad?

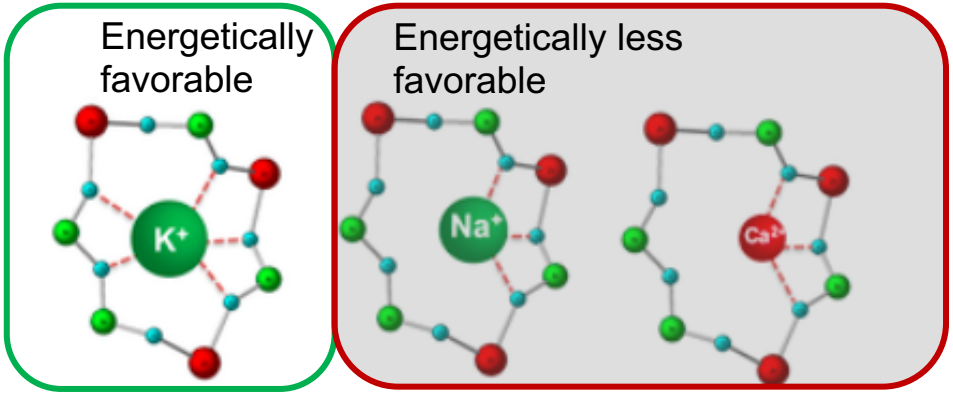
Causes:
- Kidney disease
- Heart failure
- Alcohol/drug abuse
- Type 1 diabetes
- ACE, ARB side effects

Treatments:
- Low K^+ diet
- K^+ binders
- Dialysis



Sodium zirconium cyclosilicate (SZC, *LOKELMA®*)

- Orally-administered suspension
- **Insoluble** crystal that binds K^+ ions from solution
- **Not absorbed** from the gastrointestinal tract into the circulation
- Highly specific for K^+ ions
- Binds intestinal K^+, prevents absorption, creates a gradient to pull K^+ out of circulation
- Applications for acute and chronic potassium reduction

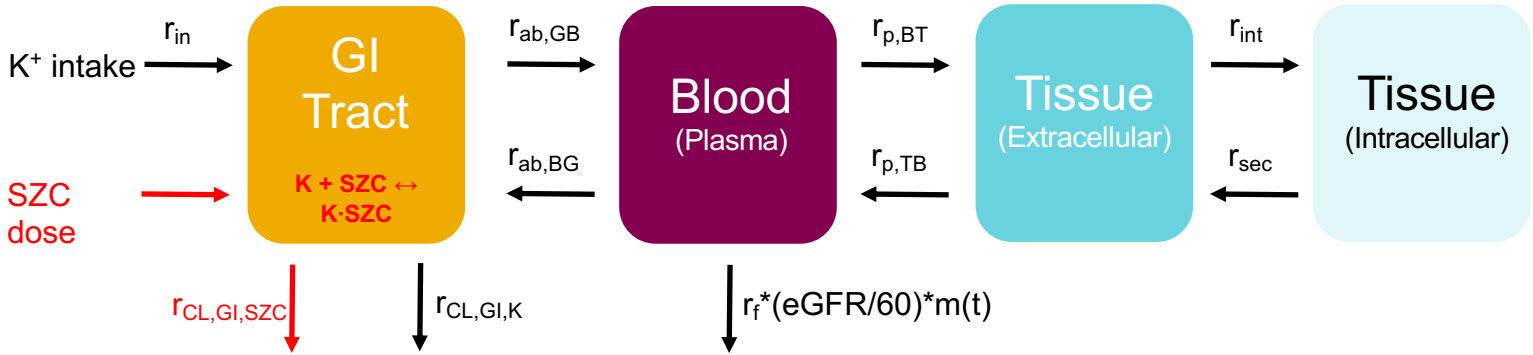


A QSP model was needed to understand SZC mechanism of action and to address clinical questions in late-stage development and clinical trial design

- The redistribution and excretion of potassium in patients treated with SZC are not fully understood
- Many clinical questions regarding clinical trial design, dose regimen confirmation and safety/manufacturing have been raised

Base case: SZC was developed for chronic use to lower serum K^+ in hyperkalemic subjects

A QSP model was developed to describe SZC-K⁺ binding within a framework of physiological K⁺ homeostasis (absorption, transport, disposition and excretion) in healthy and hyperkalemic subjects



- K⁺ intake: 3 meals/day (8am, noon, 6pm), 100mEq total, 25% breakfast, 33% lunch, 42% dinner
- A wide range of doses/regimens are taken into consideration: Dosing taken directly from patient data ➔ accounts for deviations from planned treatment
- Model estimation (patient specific parameter sets):
  - In-vitro SZC-K⁺ binding data
  - QSP model to individual patient plasma K⁺ data from 3 SZC clinical trials (N=1101 Patients)
  - Literature data/Physiological constraints

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Application: Safety assessment of a child resistant package

Background:

- Through a standardized test of the Lokelma sachets, it was concluded that a child may be able to open one sachet during a reasonable unattended time
- This study is designed to explore the immediate decrease in plasma [K^+] upon consumption of 1 dose of 10g by a 2-year-old child

Question: Whether additional child-resistant packaging is necessary for SZC?

Method: The QSP model was modified to represent the physiology in a 2-3 year-old child (extrapolated from the adult patient parameters)

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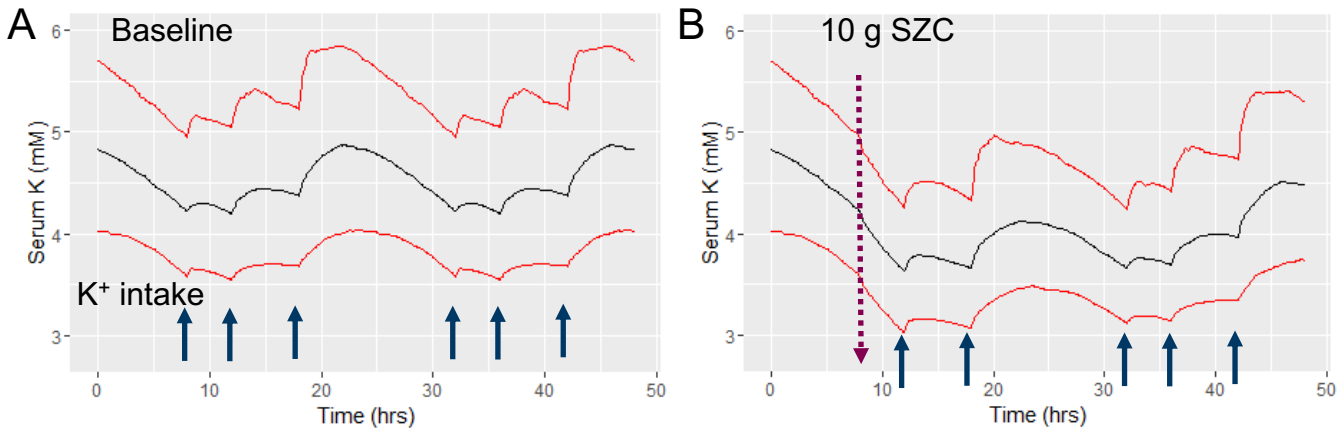
Application: Safety assessment of a child resistant package

- *Question*: Whether additional child-resistant packaging is necessary for SZC?



- Model showed that though there is an immediate reduction in plasma [K^+] following SZC ingestion, only 2.8% of the virtual population became hypokalemic (<3.0mM, trough ~ 2.95mM, duration ~0.3hr)

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Summary

- **Utility of QSP model in late stage development**
  - Within-class differentiation vs. competition (on efficacy and safety grounds)
  - MoA rationale in context of quantitative disease understanding
  - Quantitative translation across indications, across patient populations
- **Soft skill development: communication with project team to convince them of our modeling approaches/assumption/learnings**
- **Impact:** Modeling results in conjunction with clinical safety data and non-clinical toxicology data were used to show the commercial packaging met the requirements and avoided a minimum 6-month delay in US launch

Acknowledgement

- **Quantitative clinical pharmacology team at AstraZeneca**
  - Gabriel Helmlinger, Don Stanski and team
- **Collaborators at AstraZeneca**
  - M&S-Decisions, a Moscow-based modeling consultancy
  - Biosciences (preclinical)/DMPK
  - Translational science/Biomarker group
  - Bioinformatics
  - Oncology Translational Medicine Unit (clinicians)
- **PKS sciences, NIBR, Novartis**
  - Birgit Schoeberl
- **Johns Hopkins University, Winslow lab**
  - Raimond L. Winslow, Ph.D.
  - Joseph L. Greenstein, Ph.D.

ASCPT Webinar Series
Systems Pharmacology (SP) and Early Career (EC) Communities

Next Generation Pharmacometricians – Examples from Early Career Modelers on MID3 Implementation

Jan. 30th, 2020

Model Informed Drug Discovery and Development (MID3)

Characterizing Colon TNFα Suppression and Treatment Effects of an Anti-TNFα Monoclonal Antibody in a Mouse Inflammatory Bowel Disease Model:

Questions and Solutions for a Next Generation Pharmacometrician

Songmao Zheng, Ph.D., Scientific Director, Janssen Biotherapeutics, Janssen R&D

ASCPT Webinar Series (Systems Pharmacology and Early Career Communities)

Jan. 30th, 2020

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JBIO Janssen BioTherapeutics

janssen | PHARMACEUTICAL COMPANIES OF Johnson&Johnson

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Inflammatory Bowel Disease (IBD) Pathology: an Overview

- The **inflammatory bowel diseases** (Crohn's disease; ulcerative colitis) are chronic inflammatory disorders of the intestine and/or colon.

- Intestinal cells that come under stress (eg, **bacterial overgrowth, endotoxin, reactive oxygen species, allergen**) are damaged.

- This **dynamic inflammation** involves the release of **proinflammatory cytokines** and **chemokines** that perpetuate the inflammation.

- **Biologic therapies** target the proinflammatory cytokines (TNF-α and IL-12/23), or the integrins/block the adhesion of leukocytes.

Nielsen OH, Ainsworth MA. N Engl J Med 2013;369:754-762.
Ye et al., Gastroenterology. Oct 2011; 141(4): 1323–1333.
Van den Berghe N, Gils A, Thomas D. Clinical Pharmacology & Therapeutics 2019; 106:945-54.

Biologicals approved for the treatment of IBDs in the EU and/or the US

Biological	Target	Disease	Route of administration	Dosing schedule
Infliximab	TNF-α	CD/UC	i.v.	5 mg/kg at week 0, week 2, week 6, then every 8 weeks
Adalimumab	TNF-α	CD/UC	s.c.	CD: 80 or 160 mg at week 0, 40, or 80 mg at week 2, then 20 or 40 mg every 2 weeks
				UC: 160 mg at week 0, 80 mg at week 2, then 40 mg every 2 weeks
Golimumab	TNF-α	UC	s.c.	200 mg at week 0, 100 mg at week 2, then 50 mg every 4 weeks if weight < 80 kg (EU) or 100 mg every 4 weeks if weight ≥80 kg (EU and US)
Certolizumab pegol	TNF-α	CD	s.c.	400 mg at week 0, week 2, week 4, then 400 mg every 4 weeks
Natalizumab[a]	α4 integrin	CD	i.v.	300 mg at week 0, then every 4 weeks
Vedolizumab	α4β7 integrin	CD/UC	i.v.	300 mg at week 0, week 2, week 6, then every 8 weeks
Ustekinumab	IL-12/23	CD	First i.v., then s.c.	i.v. infusion of 260 mg if weight ≤ 55 kg, 390 mg if weight 55–85 kg, 520 mg if weight > 85 kg at week 0, then 90 mg s.c. every 8 weeks

Loading dose or induction phase is included in all cases.

Van den Berghe N, Gils A, Thomas D. Clinical Pharmacology & Therapeutics 2019; 106:945-54.

Objectives of the Study

Approved biologics data in IBD suggest that ***once the inflammatory burden is reduced (eg, with loading doses during disease flare)****,* ***the drug exposures required to maintain efficacy may be lower than that with initial induction****.*

Key Questions: What is the impact of IBD on:

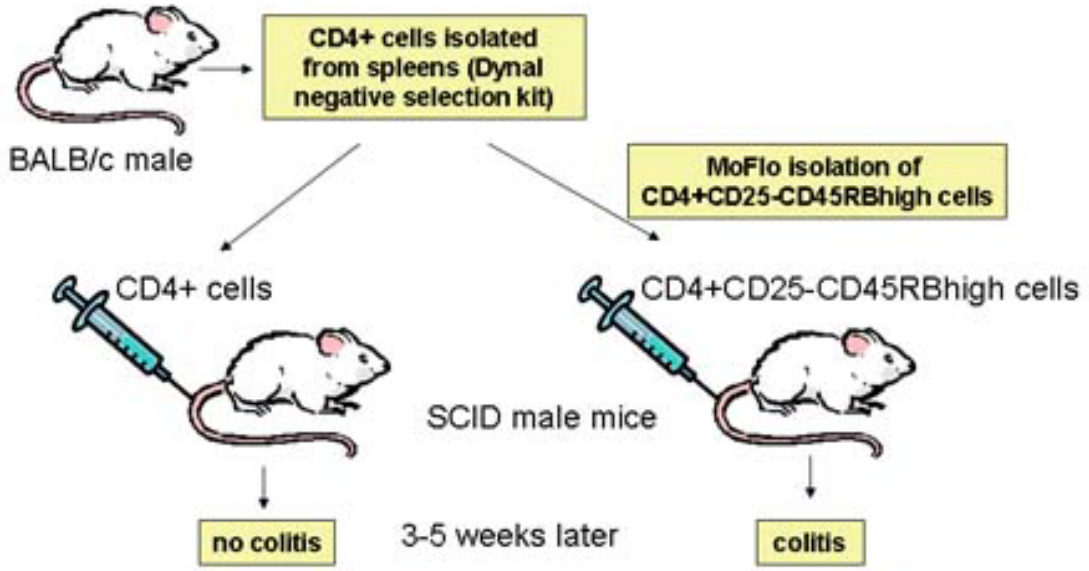
- anti-TNFα mAb disposition
- the ability of anti-TNFα mAb to neutralize TNFα at the colon
- the potential mechanism behind utilization of loading dose for treatment of IBD?

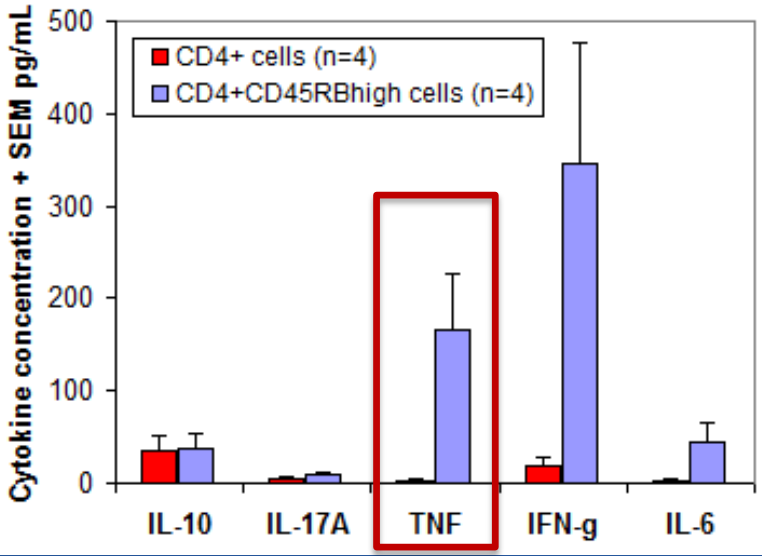
Key Challenges and Opportunities:
Questions for a Next Generation Pharmacometrician

- What **animal model** is relevant to human IBD?
- What **doses / dosing regimen** are needed?
- What experimental **endpoints and sampling** should be included?
- What type of bioanalytical **assays** are needed?
- What kind of **modeling approach** (including software) is fit-for-purpose and can provide robust parameter estimates to interpret the study findings?
- **What can be learned** from both experimental data and modeling results?

CD45RB^{high} Adoptive T Cell Transfer Model in Mice

- Adaptive transfer of **CD4^{+}CD45RB^{high} T cells** (naive T cells) from healthy wild-type (WT) mice into syngeneic recipients that lack T and B cells
  - induces a **pancolitis** and **small bowel inflammation** at 5–8 wk following T cell transfer





Am J Physiol Gastrointest Liver Physiol 305: G763–G785, 2013.

Powrie F, Leach MW, Mauze S, Caddle LB, Coffman RL. *Int Immunol* 5: 1461–1471, 1993.

T cell transfer model of chronic colitis: concepts, considerations, and tricks of the trade. Am J Physiol Gastrointest Liver Physiol. 2009;296:G135–G146.

https://hookelabs.com/services/cro/ibd/colitis_scid/

Study Design

Disease model

- Mouse T-cell transfer IBD model

Study compounds

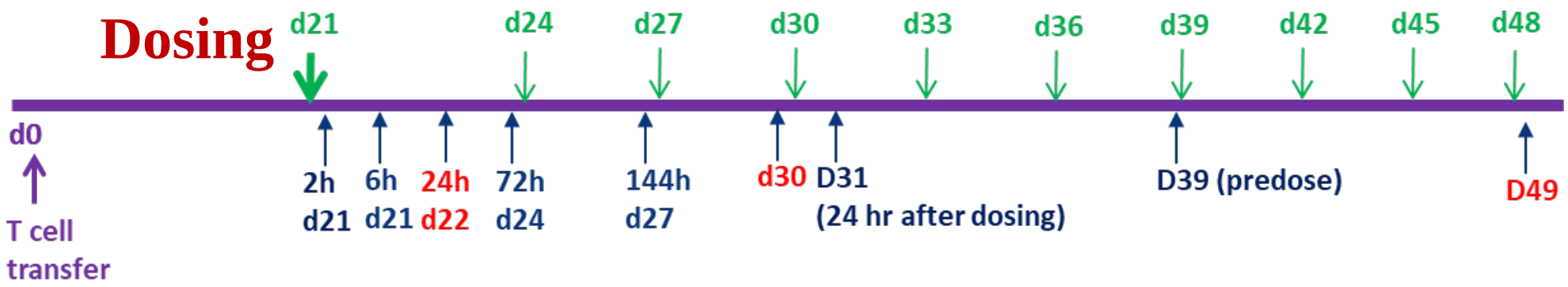
- CNTO 5048: an anti-murine TNFα surrogate mAb of golimumab (IgG1)
- CNTO 1322: isotype control

Readouts

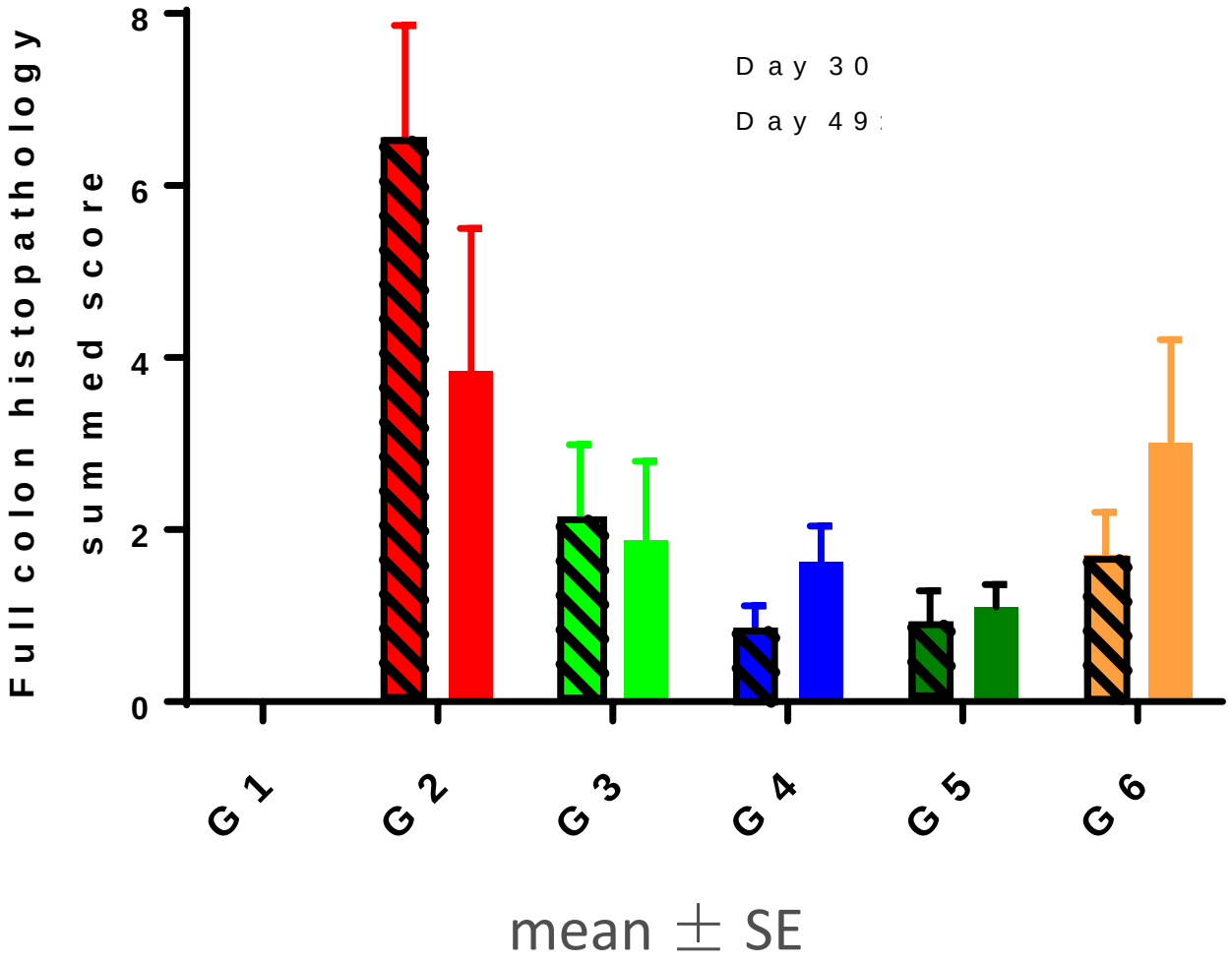
- **mAb PK:** systemic and at the tissue site (colon)
- **Target engagement:** soluble TNFα, systemic and at the tissue site (colon)
- **Disease score** including colon weight/length
- **Histopathology**

Study Design based on Prior Studies and PK Simulations

Study Group	N	Treatment	Dose
1	30	Non-IBD mice–CNTO 5048	Single i.v. 10 mg/kg
2	30	IBD mice –CNTO 5048	Single i.v. 10 mg/kg
3	18	IBD mice – Isotype control	10mg/kg i.v. loading dose +9* 0.3mg/kg Q3D i.p. maintenance dose
4	22	IBD mice – CNTO 5048	10mg/kg i.v. loading dose +9* 0.3mg/kg Q3D i.p. maintenance dose
5	22	IBD mice – CNTO 5048	1.4mg/kg i.v. dose +9* 1.4mg/kg Q3D i.p. maintenance dose
6	22	IBD mice – CNTO 5048	0.3mg/kg i.v. dose +9* 0.3mg/kg Q3D i.p. maintenance dose

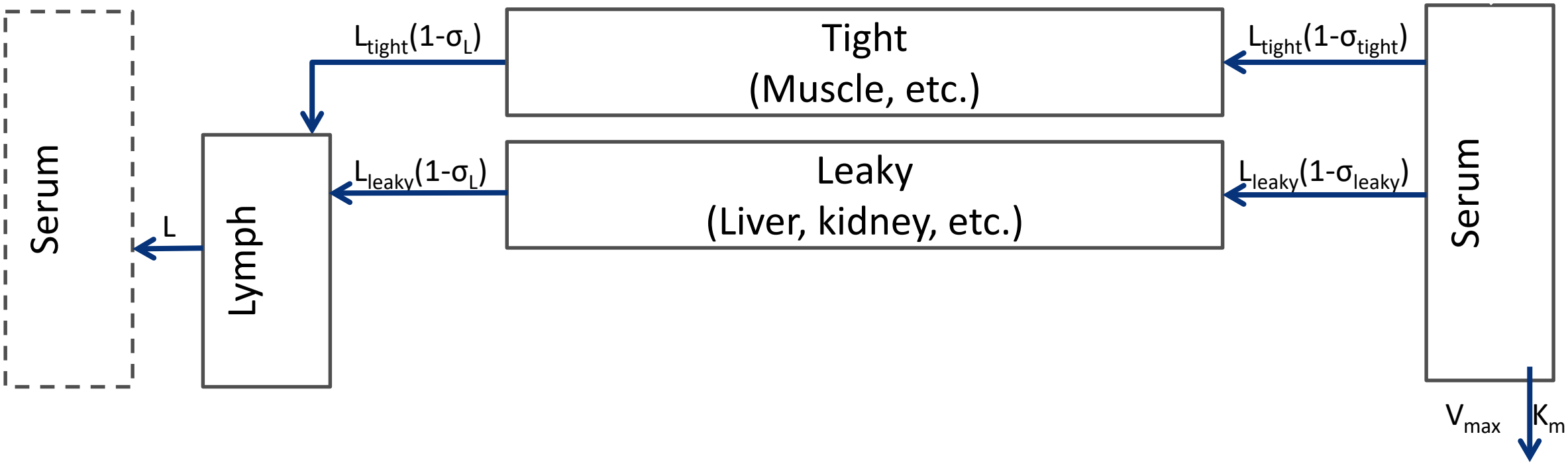


Summary of Representative Experimental Observations



- G1: Non-IBD mice (without CD45RB^{high} T cell transfer), CNTO 5048 (10 mg/kg)
- G2: IBD mice (+ CD45RB^{high} T cell transfer), isotype control (1x 10 + 9x 0.3 mg/kg)
- G3: IBD mice, CNTO 5048 (1x 10 mg/kg)
- G4: IBD mice, CNTO 5048 (1x10 + 9x0.3 mg/kg)
- G5: IBD mice, CNTO 5048 (10x 1.4 mg/kg)
- G6: IBD mice, CNTO 5048 (10x 0.3mg/kg)

Step-wise Model Building



mPBPK/PD model was developed to characterize CNTO 5048 PK and disposition, colon soluble TNFα target engagement (TE) and PD effect

Cao Y, Jusko WJ. J Pharmacokinet Pharmacodyn 2012; 39:711-23.
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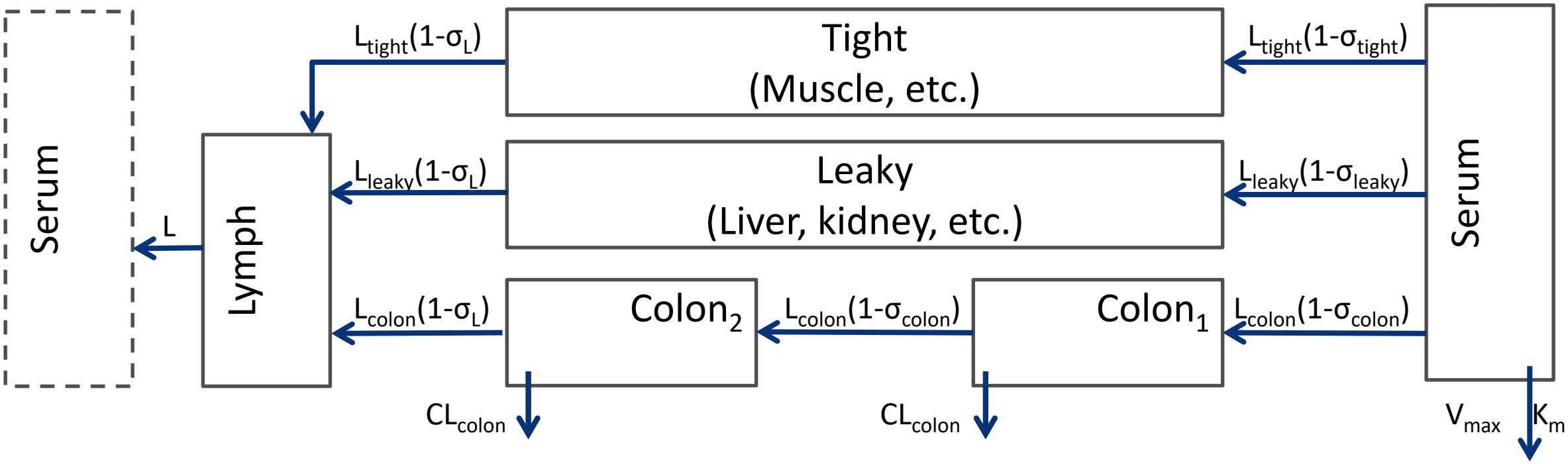

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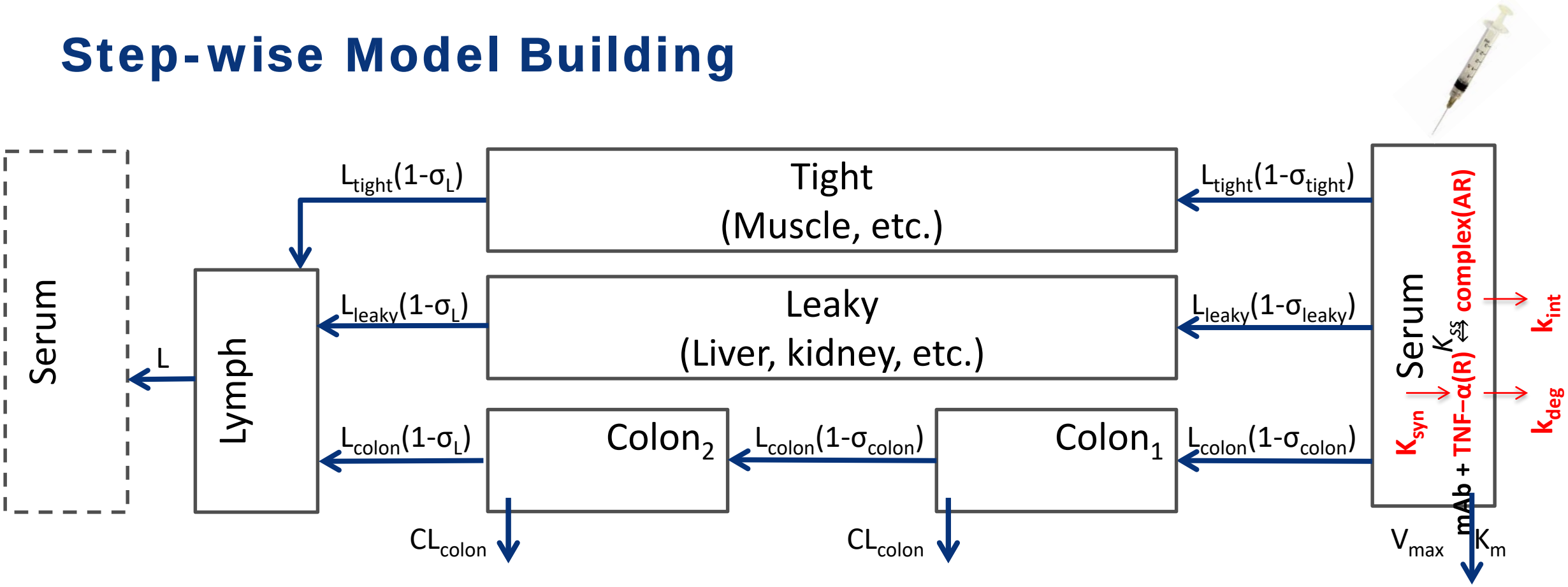

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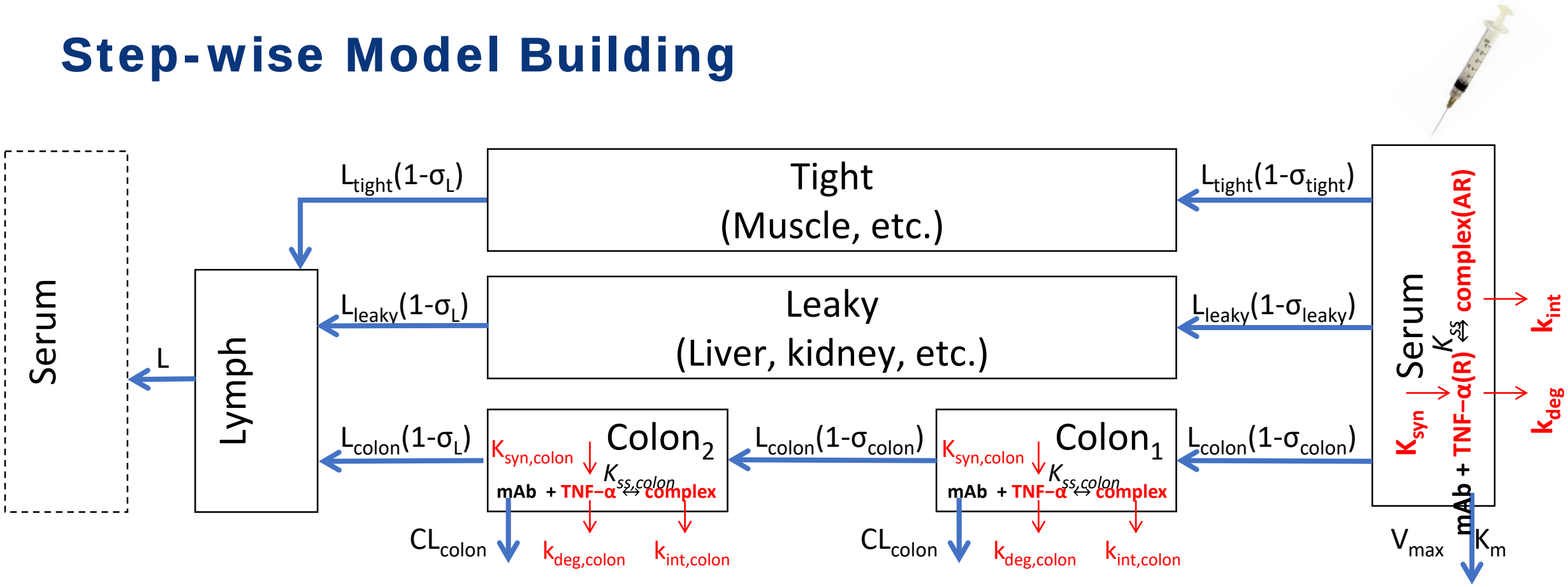

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Modeling Software and Methods

- Model fitting was performed with **Monolix 2019R1** using **naive pooling** of data.
- **Importance sampling algorithm** was used to calculate likelihood and Stochastic Approximation was used to derive Fisher information matrix.
- The **proportional residual error model** was used for serum CNTO 5048 concentrations; **constant residual error models** were used for colon concentrations of CNTO 5048, serum and colon TNFα concentrations.
- **Model performance** was evaluated by goodness-of-fit plots and -2 log likelihood value (-2LL).

Key Model Parameters

Parameter	Definition
V_s [a]	Serum volume
ISF [a]	Volume of total interstitial space fluid
V_{lymph} [a]	Lymph volume
L [a]	Total Lymph flow rate
σ_L [a]	Reflection coefficient for lymph
$V_{max,nonIBD}$	Antibody elimination rate capacity in serum for non-IBD mice
$V_{max,IBD}$	Antibody elimination rate capacity in serum for IBD mice
K_m	Apparent affinity for antibody elimination
σ_{tight}	Reflection coefficient for tight tissues
σ_{leaky}	Reflection coefficient for leaky tissues
k_a	First-order ate constant for i.p. absorption
$\sigma_{colon,nonIBD}$	Reflection coefficient for colon in non-IBD mice
$\sigma_{colon,IBD}$	Reflection coefficient for colon in IBD mice
$CL_{colon,nonIBDhy}$	Clearance of antibody from colon in non-IBD mice
$CL_{colon,IBD}$	Clearance of antibody from colon in IBD mice
$V_{colon,nonIBD}$ [b]	ISF volume of colon in non-IBD mice
$V_{colon,IBD}$ [b]	ISF volume of colon in IBD mice
$L_{colon,nonIBD}$ [b]	Lymph flow rate of colon in non-IBD mice
$L_{colon,IBD}$ [b]	Lymph flow rate of colon in IBD mice
k_{deg}	Degradation/Turnover rate constant for TNFα in serum
k_{int}	Internalization (elimination) rate constant for CNTO5048–TNFα complex in serum
R_0 [c]	Baseline concentration of TNFα in serum in IBD mice
K_{ss}	Quasi-equilibrium binding constant for CNTO5048 and TNFα in serum
$k_{deg,colon}$	Degradation rate constant for TNFα in colon ISF
$k_{int,colon}$	Internalization rate constant for CNTO5048–TNFα complex in colon ISF
$R_{0,colon}$ [c,d]	Baseline concentration of TNFα in colon ISF in IBD mice
$K_{ss,colon}$	Quasi-equilibrium binding constant for CNTO5048 and TNFα in colon ISF

35 equations (including derived equations) were used for the final model.

References for parameters

- Cao Y, Balthasar JP, Jusko WJ. J Pharmacokinet Pharmacodyn 2013; 40:597-607.
- Chen X, Jiang X, Doddareddy R, Geist B, McIntosh T, Jusko WJ, et al. J Pharmacol Exp Ther 2018; 365:140-55.
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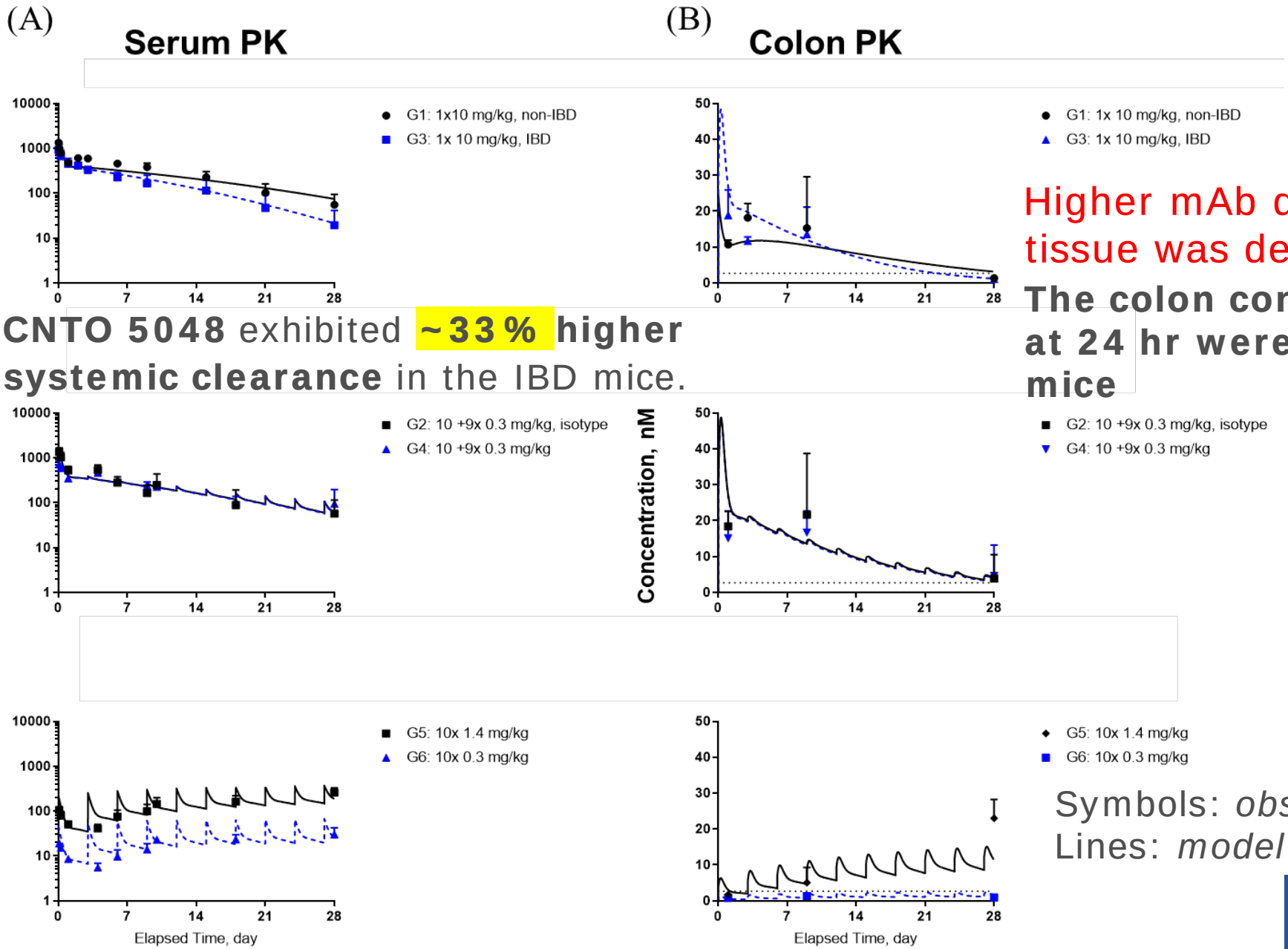
- Naeem M, Choi M, Cao J, Lee Y, Ikram M, Yoon S, et al. Drug design, development and therapy 2015; 9:3789-99.

Model fitting for CNTO 5048 in Serum or in Colon Homogenate



- **CNTO 5048** exhibited **~33% higher systemic clearance** in the IBD mice.

Higher mAb distribution to inflamed tissue was demonstrated.

The colon concentrations of CNTO 5048 at 24 hr were ~2-fold higher in the IBD mice

Symbols: *observed mean (SD)*
Lines: *model prediction*

Key Learnings from PK Modeling

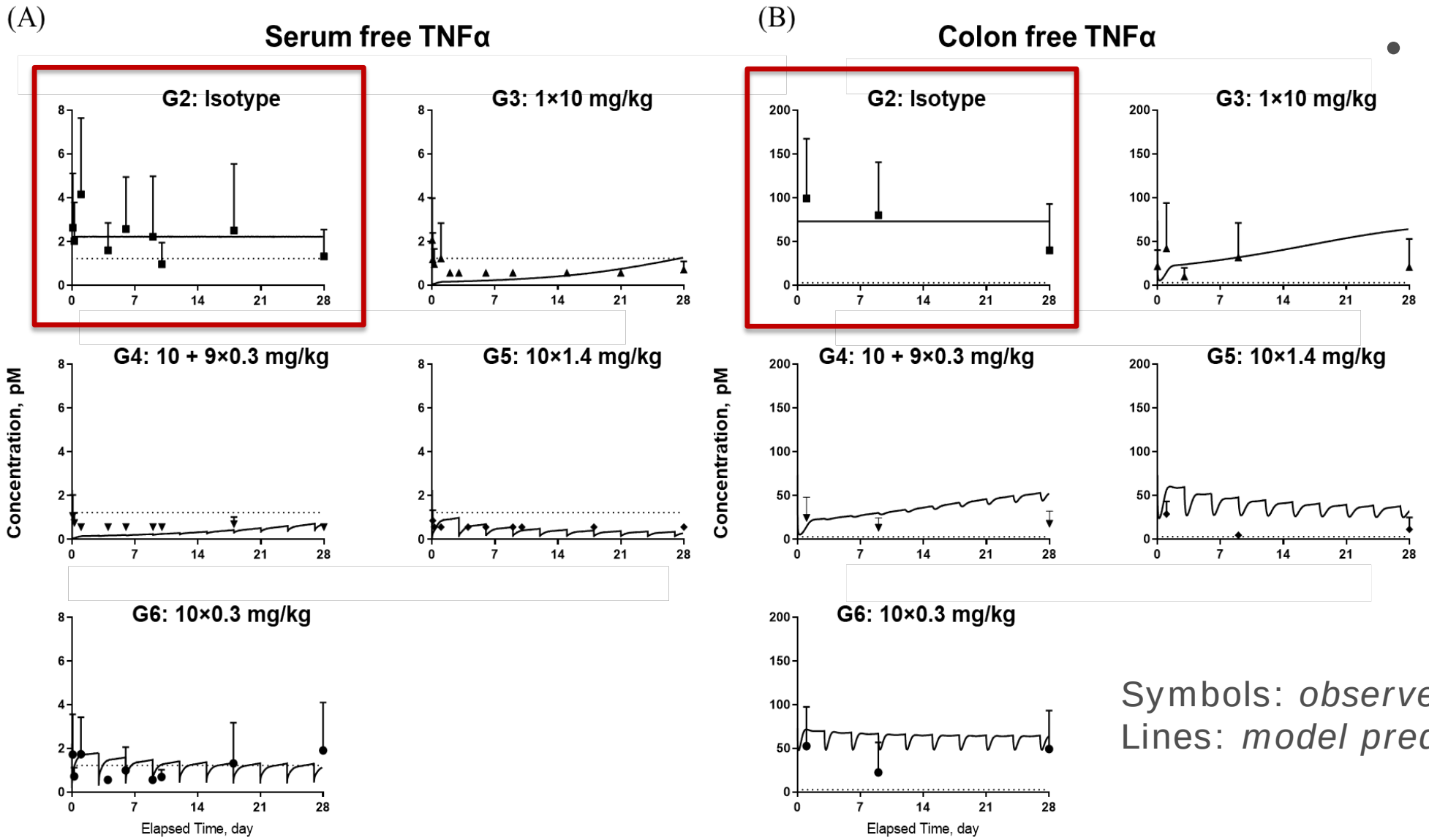
- **Inflammatory diseases such as IBD can increase vascular permeability and change mAb disposition.**

- Previous mPBPK modelling work had suggested that **convection and lymph drainage** are the dominant pathways for biologics' uptake and removal from tissues.

- Consistently, the **model-estimated clearance of CNTO 5048 from colon ISF** compartment in the IBD mice was similar to the reported **lymph flow rate** in IBD mice.

- Chen X, Jiang X, Jusko WJ, Zhou H, Wang W. J Pharmacokinet Pharmacodyn 2016; 43:291-304.
- Chen X, Jiang X, Doddareddy R, Geist B, McIntosh T, Jusko WJ, et al. J Pharmacol Exp Ther 2018; 365:140-55.

Model fitting for Free TNFα in Serum and in Colon Homogenate



- Calculated baseline TNFα in colon ISF was ≈**200-fold higher** than serum, indicating that **colon TNFα mainly comes from local secretion.**

Symbols: *observed mean (SD)*
Lines: *model prediction*

Key Learnings from PK/TE Modeling

- The **Ksyn** of TNFα in colon was estimated to be ~17-fold higher than that in serum.

- CNTO 5048 bound to TNFα in both serum and colon ISF and form mAb/TNFα complexes.
  - ✓ Serum Kel for **CNTO 5048/TNFα complex** was substantially lower than **Kdeg** of free TNFα, but considerably higher than the free antibody.
  - ✓ Possibly related to **larger complex formed between trimeric TNFα and the bivalent mAbs**

Key Learnings from PK/TE Modeling

- The estimated *in vivo* quasi-equilibrium constant between CNTO 5048 and TNFα in serum and in colon were both similar to the *in vitro value*.

- The **Kdeg for free TNFα in serum** was estimated and corresponded to a half-life ($t_{1/2}$) of 3.3 min which was within 2-fold of the reported ~6 to 7 min $t_{1/2}$ of radiolabelled mouse TNFα in mice serum.

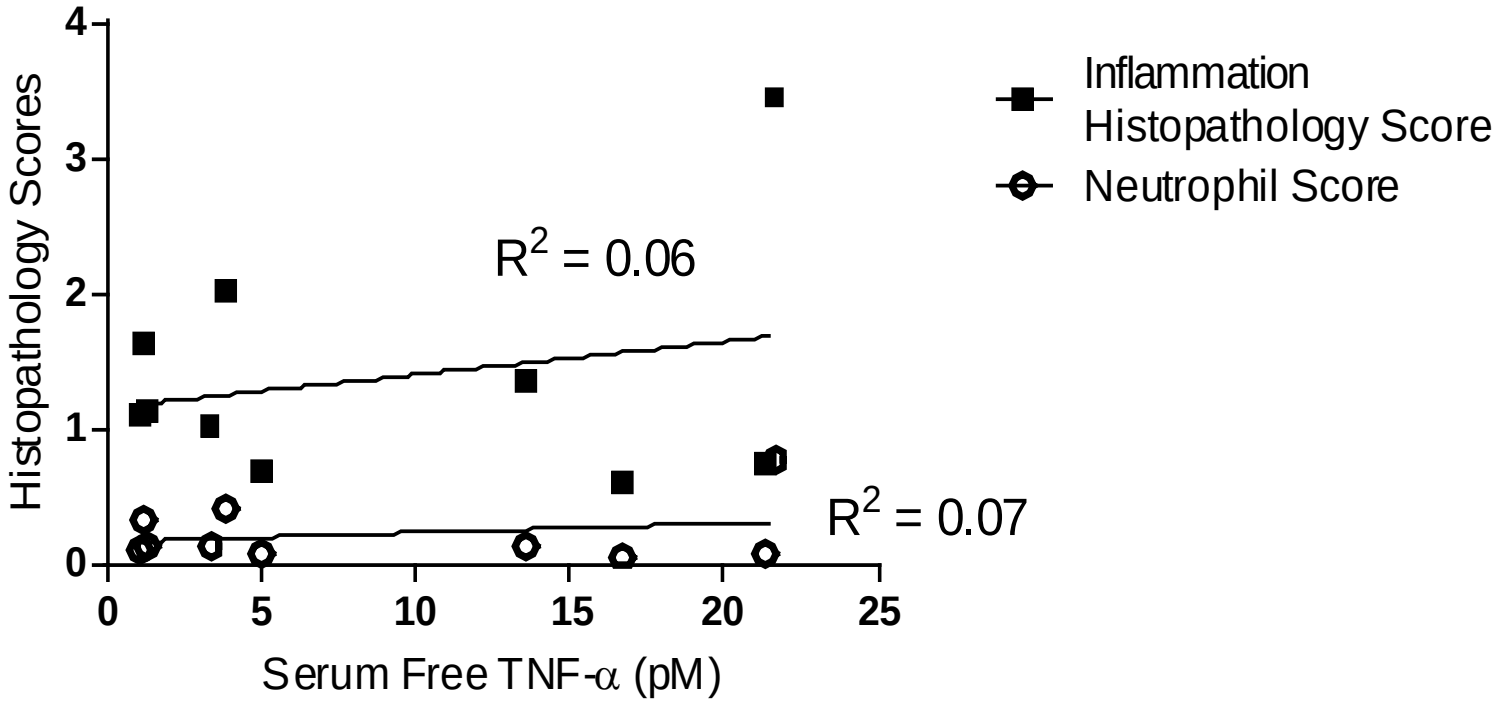
- The **Kdeg for free TNFα in colon** was estimated to be ~10-fold lower than that in serum.

- The elimination of **CNTO 5048/TNFα complex in colon** was also likely mediated by lymph drainage based on parameter estimates.

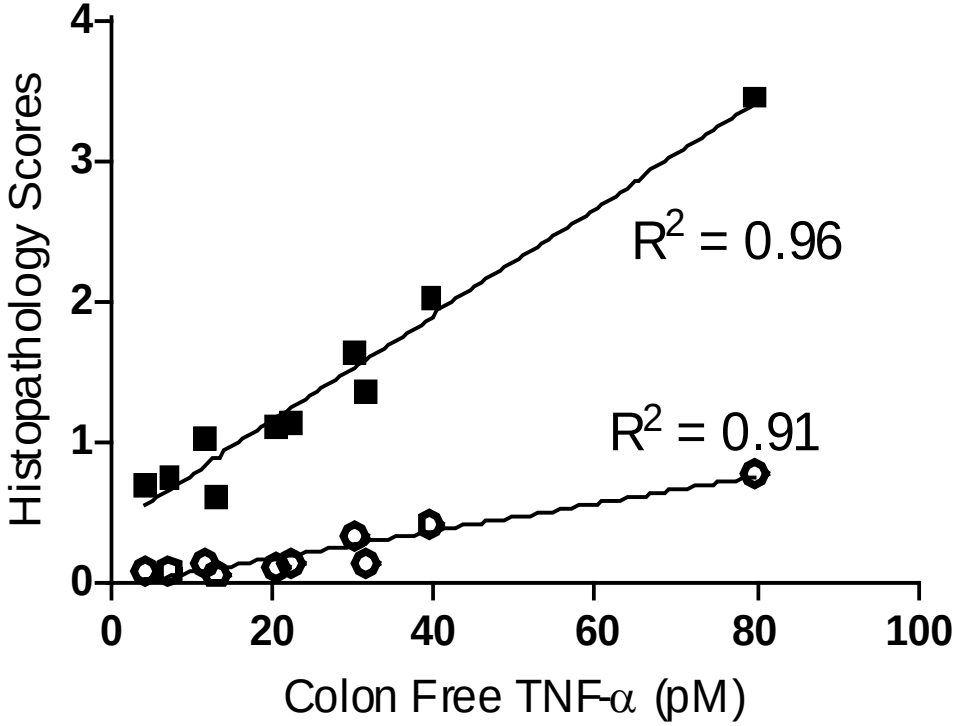
Chen X, Jiang X, Jusko WJ, Zhou H, Wang W. J Pharmacokinet Pharmacodyn 2016; 43:291-304.
Beutler BA, Milsark IW, Cerami A. J Immunol 1985; 135:3972-7.

Correlations between Free TNFα in Colon or Serum versus Inflammation Histopathology Scores or Neutrophil Scores

Free TNF-α in serum *vs* Scores



Free TNF-α in colon *vs* Scores



Free TNFα concentrations in colon, but not in serum were shown to correlate well with the colon histopath results.

Key Learnings related to Loading Doses

- **The PK/TE assessments provided evidence to support the potential benefit of loading dose in IBD treatment.**

- **First, higher mAb distribution to inflamed tissue was demonstrated.**
  - ✓ *Previous studies demonstrated mucosal healing in IBD patients treated with biological agents*
  - ✓ *The reflection coefficient for colon in IBD mice estimated to be significantly lower than in non-IBD mice*

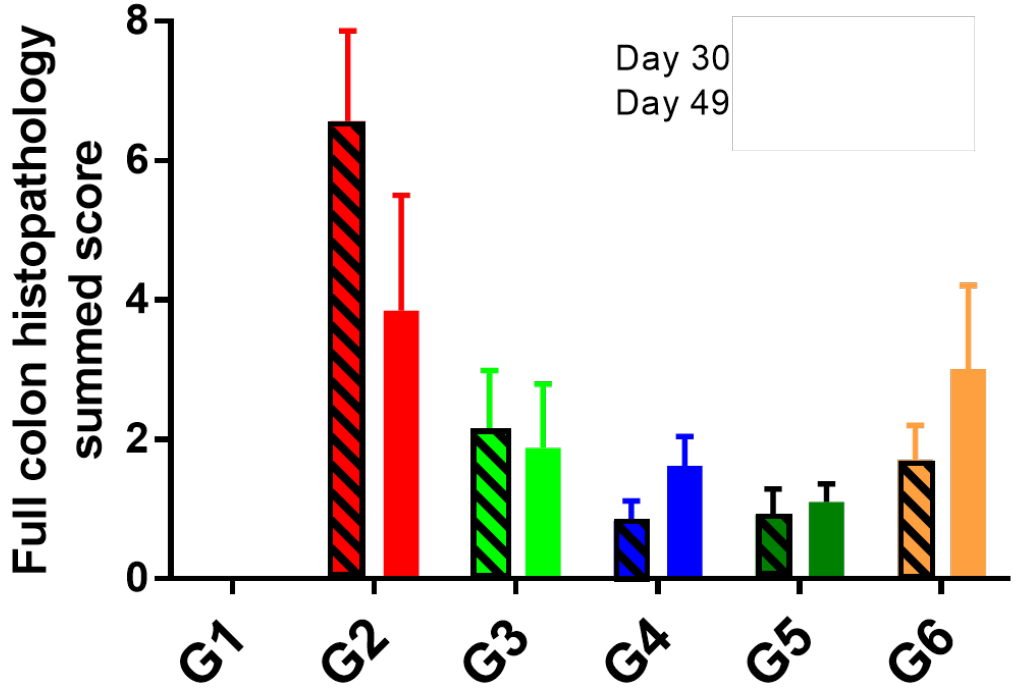
- **Second, the importance of neutralizing TNFα at colon for IBD and higher TNFα production in inflamed colon was demonstrated.**
  - ✓ *The baseline TNFα in IBD colon shown to be >26 times higher*

Key Learnings related to Loading Doses

- Results from the **isotype control treated IBD** showed a trend of reduction in colon TNFα with **natural healing of disease**.

- **G6 (10× 0.3 mg/kg)** with continuous suboptimal colon TNFα suppression showed a trend of increased inflammation.

- Suggested **the importance of rapid and complete TNFα suppression in IBD treatment:**
  - ✓ **insufficient suppression of TNFα may allow continuous exacerbation of inflammation**



Conclusions and Limitations:

- ✓ *The disposition of an anti-TNFα mAb and TNFα TE were characterized in a mouse model, and a mPBPK/PD model was developed.*
  - ✓ *insights on the rationale of using loading doses for treating IBD*
- ✓ *The value of assessing TNFα neutralization at the site of action as a biomarker was demonstrated.*

Sparse sampling for colon PD and **the temporal change of inflammation after colon TNFα suppression cannot be evaluated fully**.

Impact:

- ✓ *Advancement towards **understanding the MOAs of anti-TNFα mAbs in IBD and clinical dosing strategies for internal programs***
- ✓ *Enhanced study designs and analyte selections towards **drug design/discovery for IBD***

Key Challenges and Opportunities:
Solutions for a Next Generation Pharmacometrician

- **What animal model is relevant to human IBD?**
  - ✓ Extensive literature reading followed by talking to experts
- **What doses/dosing regimen are needed?**
  - ✓ Consulting with internal experts who had used this animal model; PK simulations
- **What experimental endpoints and sampling should be included?**
  - ✓ Extensive communication with the CRO
  - ✓ Have the “end-goals” in mind; “fit-for-purpose” experimental design
- **What type of bioanalytical assays are needed?**
  - ✓ Discussions with PK and TE assay experts
  - ✓ Consider what is a “must-have” for modeling and data interpretation
- **What kind of modeling approach (including software) is fit-for-purpose and can provide robust parameter estimates to interpret the study findings?**
  - ✓ Extensive survey of literature
  - ✓ Applied mathematics/mechanism-based modeling: evaluate the necessary complexities
  - ✓ In-depth evaluation of modeling tools and algorithms
  - ✓ Cross-check parameter estimates; model-fitting diagnostics
- **What can be learned from both experimental data and modeling results, and how to apply the learnings?**
  - ✓ Reality check with human data and clinical experiences
  - ✓ Communications with clinical pharmacologists and clinicians
  - ✓ Brainstorm with antibody engineers for future molecules

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