MODELING WITHOUT BORDERS

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Session 3b: Don't Forget the Children, How Quantitative Systems Pharmacology can Reshape Extrapolation in Pediatric Drug Development

Chairs:

Tarek Leil, Bristol-Myers Squibb
Scott Siler, DILIsym Services

Lynn Yao	Pediatric Extrapolation: Regulatory Considerations
Satyaprakash Nayak	QSP modeling of the Gaucher disease can substitute clinical trial efficacy data in pediatrics
Stephan Schaller	An integrated PB-QSP platform for the evaluation of the effects of age in diabetes
Christina Friedrich	Using a QSP model of bile acid dynamics to investigate ursodiol dynamics in neonates

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Session 3b: Don't Forget the Children, How Quantitative Systems Pharmacology can Reshape Extrapolation in Pediatric Drug Development

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Using QSP modeling to support pediatric drug development: case studies in bile acids and immuno-oncology

Christina Friedrich

Rosa & Co LLC

Acknowledgments

Immuno-Oncology Case

- Mike Reed
- Rebecca Baillie
- Rukmini Kumar
- Toufigh Gordi
- Min Zhu
- Theresa Yuraszeck
- Indrajeet Singh
- Matthias Klinger

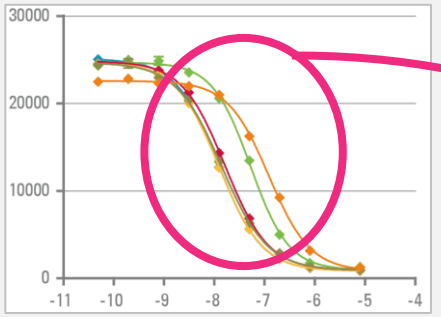
Bile Acids Case

- Toufigh Gordi
- Rebecca Baillie
- Le T. Vuong
- Saira Abidi
- Stephen Dueker
- Herbert Vasquez
- Priscilla Pegis
- Andrew O. Hopper
- Gordon G. Power
- Arlin B. Blood

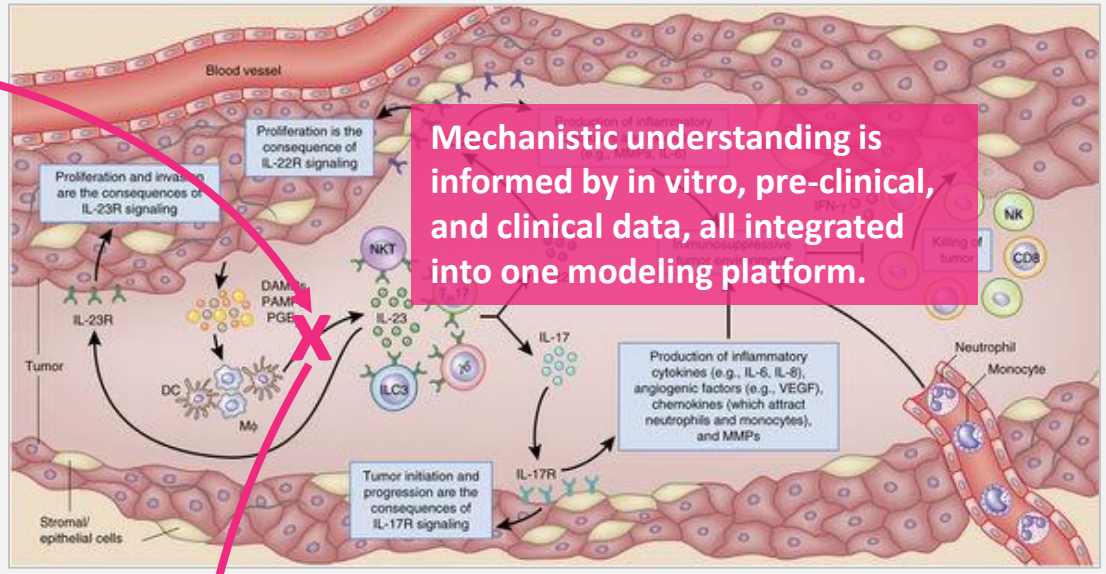
QSP helps reduce risk by improving understanding of how drug activity influences clinical outcomes.

ROSA

Preclinical Evidence

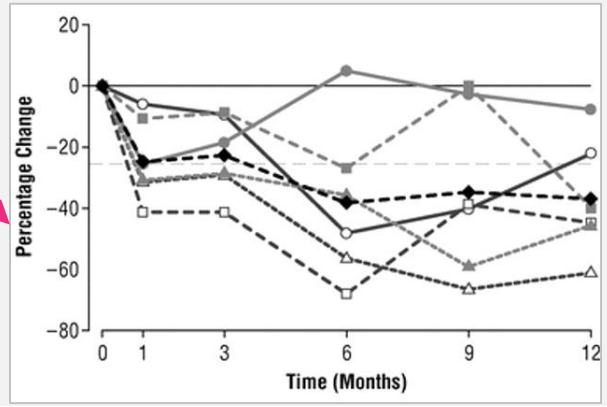


Mechanistic Understanding



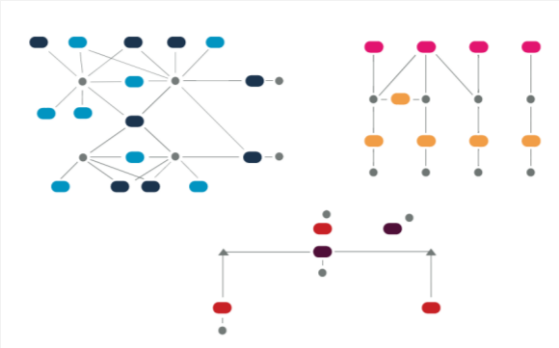
Mechanistic understanding is informed by in vitro, pre-clinical, and clinical data, all integrated into one modeling platform.

Clinical Outcome

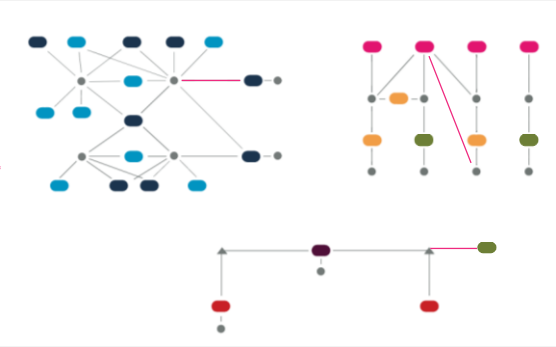


QSP modeling can inform pediatric drug development.

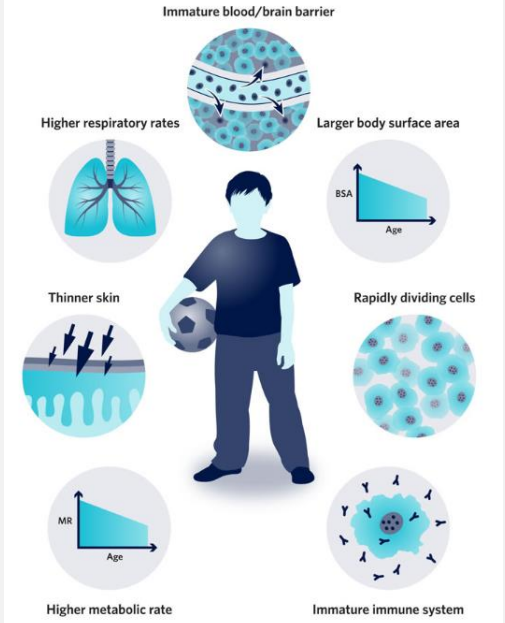
Adult QSP model



Pediatric QSP model



Differences between adult and child physiology



https://www.rch.org.au/studentorientation/Differences_between_children_and_adults/

- *Does this mean QSP can or should replace clinical trials in children?*

"It depends…

…on the context"

Recent efforts begin to define what “context” means.

Citation: CPT Pharmacometrics Syst. Pharmacol. (2019) 8, 340–343; doi:10.1002/psp4.12409

PERSPECTIVE

A Flexible Approach for Context-Dependent Assessment of Quantitative Systems Pharmacology Models

Saroja Ramanujan[1]*, Jason R. Chan[2], Christina M. Friedrich[3] and Craig J. Thalhauser[4]

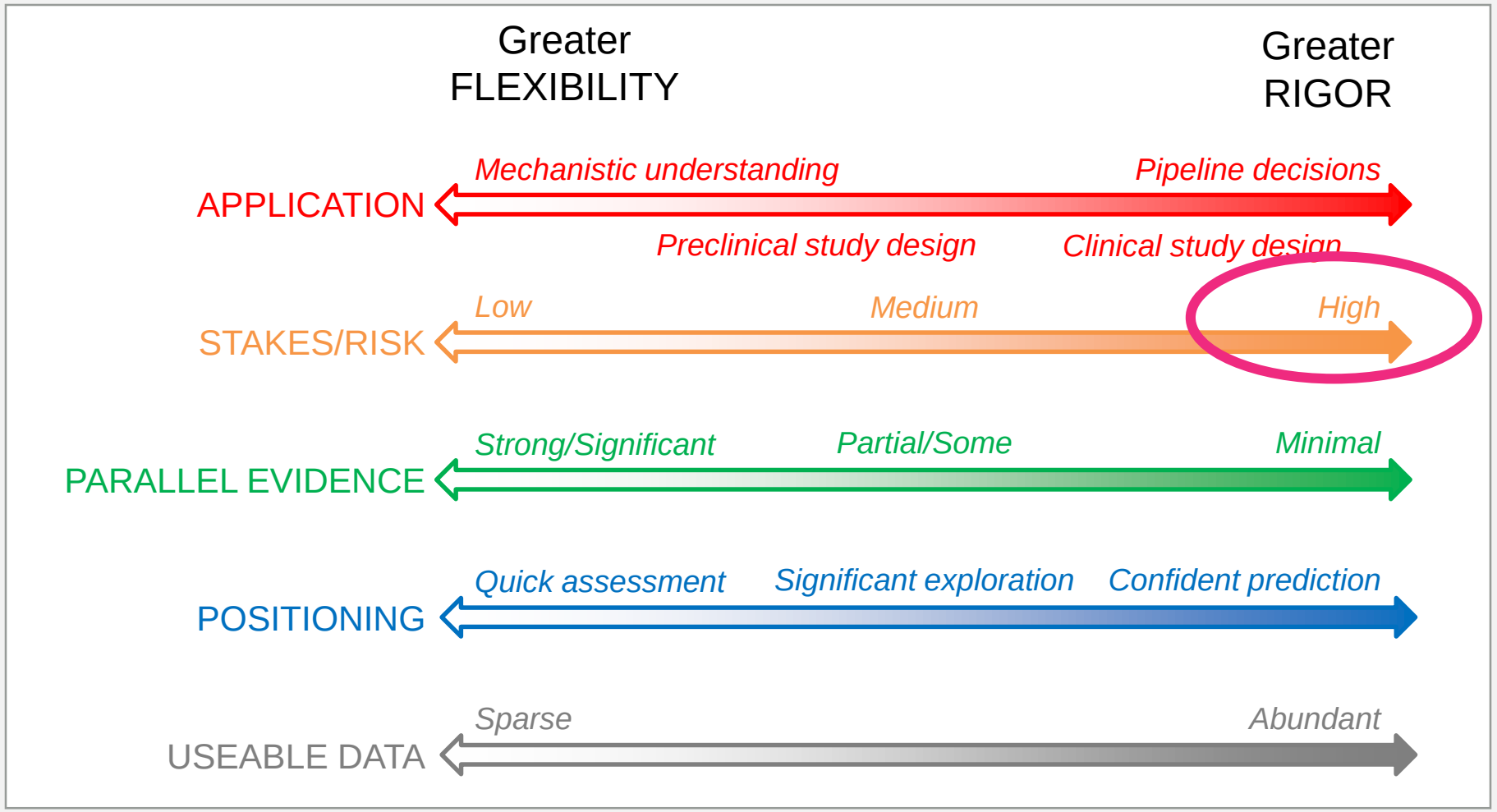
Systems pharmacology models are having an increasing impact on pharmaceutical research and development from preclinical through postapproval phases, including use in regulatory interactions. Given the wide diversity among the models and the contexts of use, a common but flexible strategy for model assessment is needed to enable the appropriate interpretation of model-based results. We present an approach to evaluate these models and discuss how it can be customized to available data and intended application.

BIOLOGICAL RELEVANCE

Assessment of the biological relevance is of critical importance in QSP, where utility requires that the biology included is appropriate to address the problem at hand and reflects relevant knowledge, data, and literature. Thus, literature support and input from biological and clinical experts are valuable in assessment. Mechanisms, hypotheses, behaviors, and phenotypes of interest should be articulated to ensure the adequacy of biological scope. QSP models typically include the representation of targets, drugs, biomarkers, and outcomes of interest. Although the scale, breadth,

Ramanujan SR, et al.
CPT:PSP 2019 Jun;8(6):340-343.

QSP modeling and qualification for pediatric population MAY call for a high degree of rigor in some contexts.



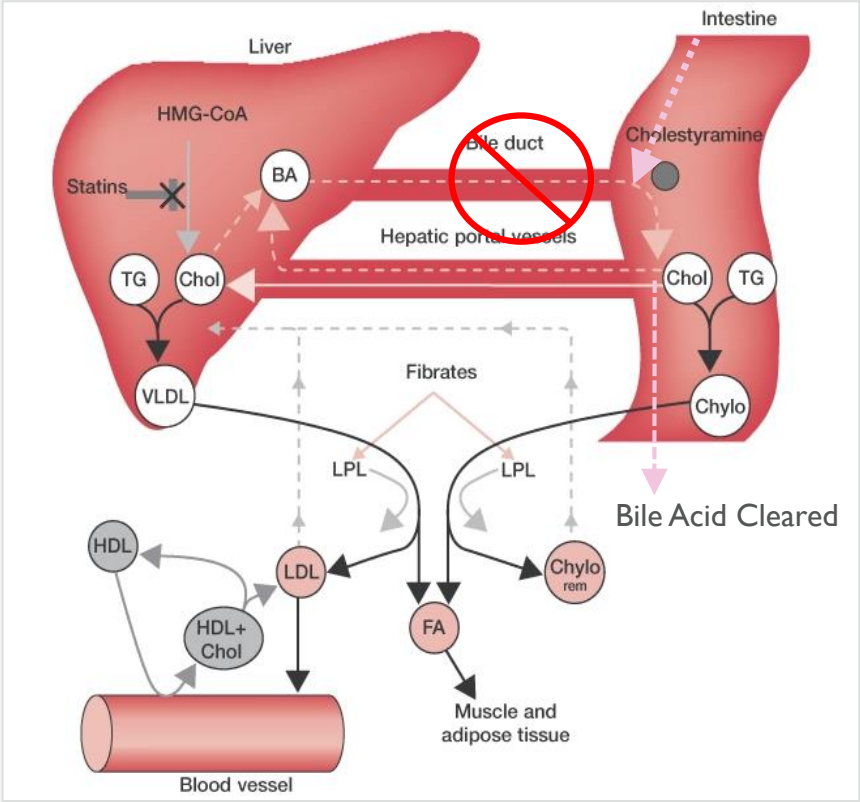
- Most QSP modeling for pediatric populations is not high risk

Ramanujan SR, et al.
CPT:PSP 2019 Jun;8(6):340-343.

Case Example 1:
Ursodiol Treatment in Neonates

The bile acid ursodiol was under investigation for treating neonatal cholestasis.

- Original project goal:
  - Model ursodiol PK to support approval for use in neonatal cholestasis
  - Ursodiol had been used off-label with ~50% response
- Data:
  - Five infants in the ICU for **non-GI related illness** received three microdoses of labeled ursodiol
  - Serum was analyzed by Accelerator Mass Spectrometry (AMS)



Ashley and Niebauer (2004) 5. Coronary artery disease. Cardiology Explained. London, Remedica. [cited 8/4/2010].

The Journal of Clinical Pharmacology
Official Publication of the American College of Clinical Pharmacology

Pediatric Pharmacology

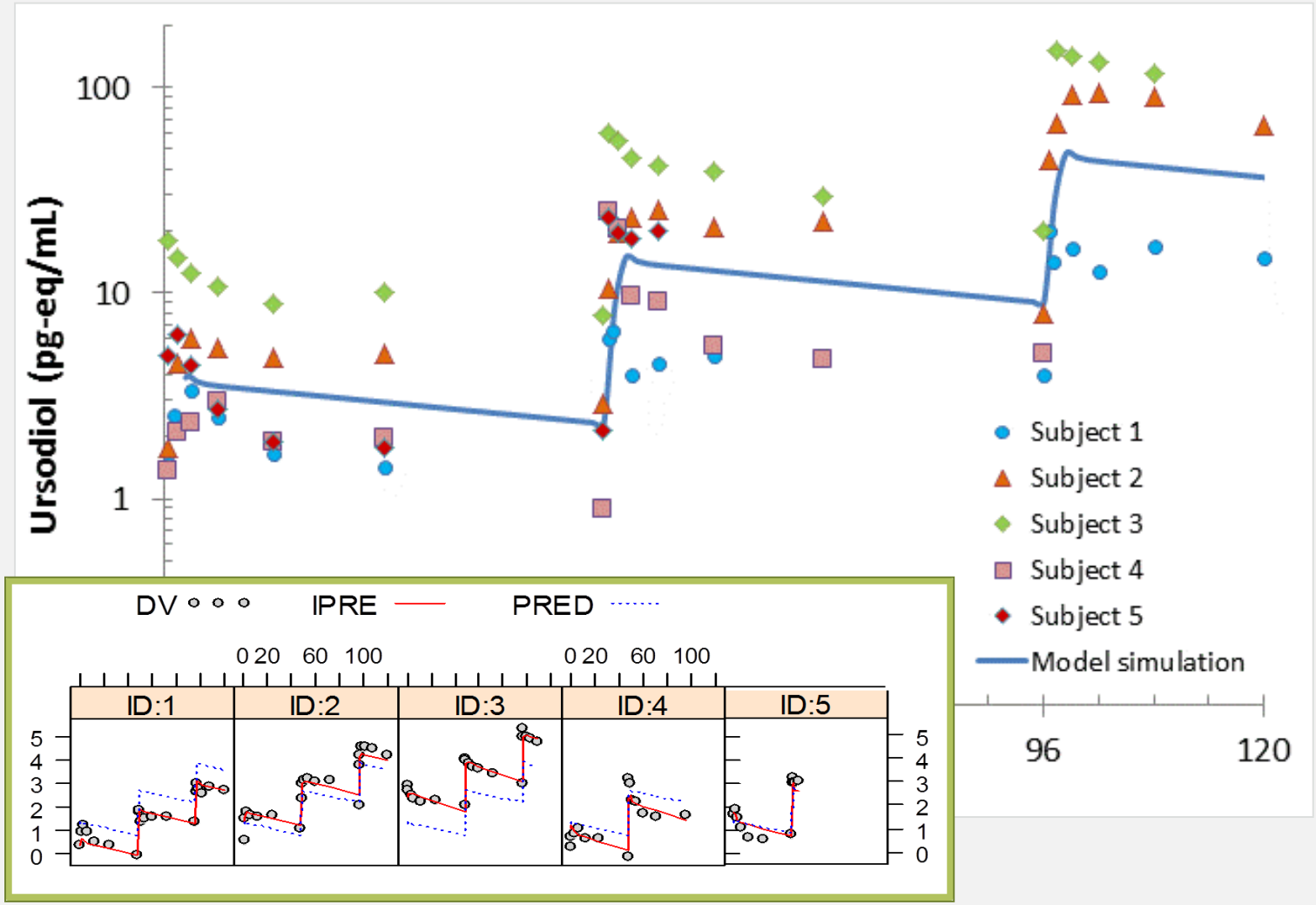
Pharmacokinetic analysis of ^{14}C-ursodiol in newborn infants using accelerator mass spectrometry

Toufigh Gordi PhD, Rebecca Baillie PhD, Le T. Vuong PhD, Saira Abidi BS, Stephen Dueker PhD, Herbert Vasquez MD, Priscilla Pegis RN, Andrew O. Hopper MD, Gordon G. Power MD, Arlin B. Blood PhD ... See fewer authors

First published: 07 May 2014 | https://doi.org/10.1002/jcph.327 | Cited by: 10

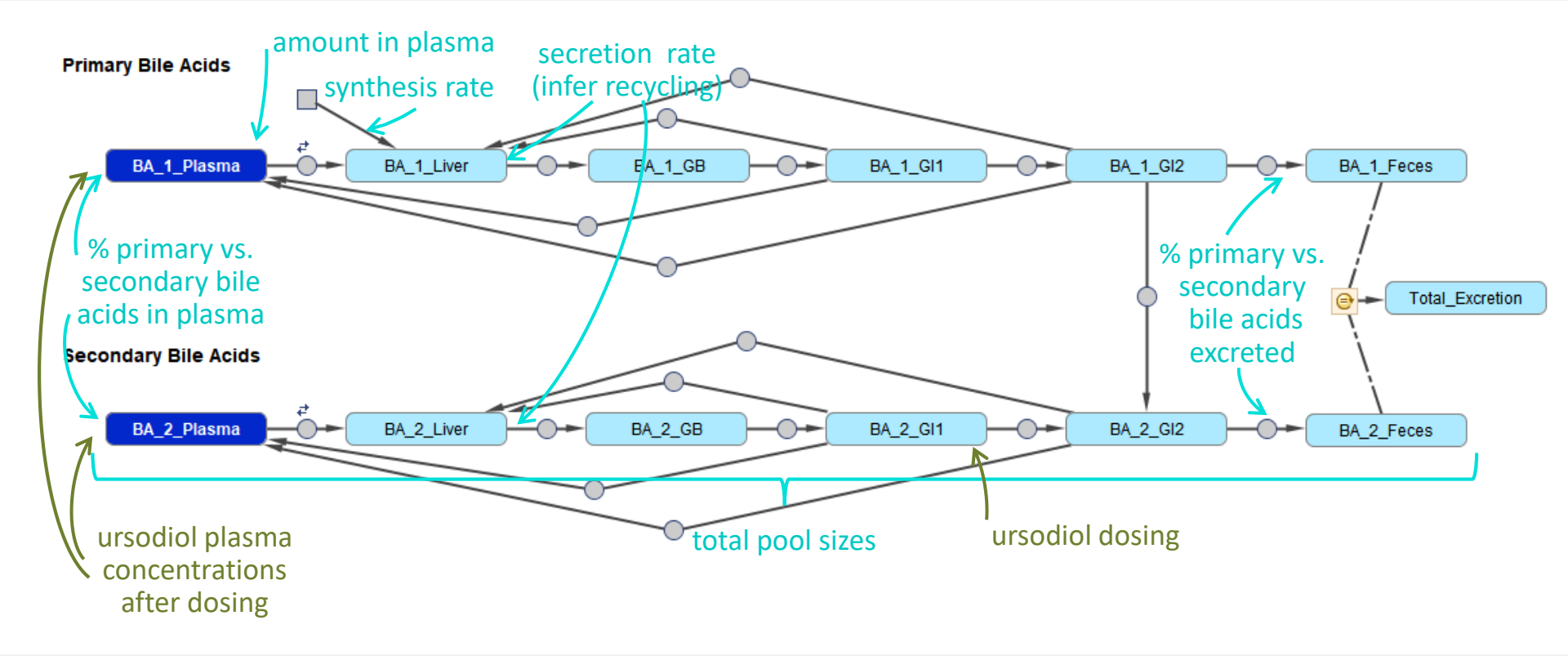
Plasma concentration data suggest a large interindividual variability.

^{14}C-Ursodiol concentration compared to lower limit of quantification



- Demographic covariates did not explain observed variability
- Shapes of ursodiol curves were notably different
- Rosa initiated an internal project to investigate

Literature data were used to calibrate the adult Bile Acids QSP model.



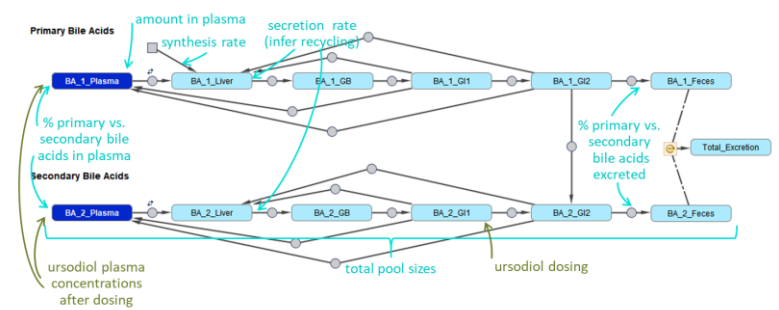
Model diagram shown in MATLAB SimBiology software.

- Most literature data are in adults

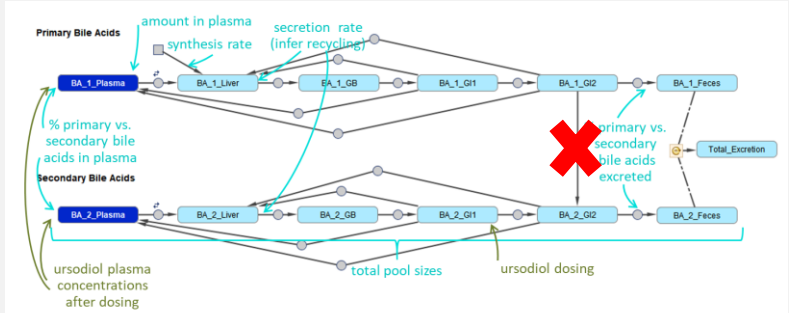
Insights can be derived from targeted changes to the adult model to emulate the neonate state.

ROSA

Adult QSP model



Pediatric QSP model

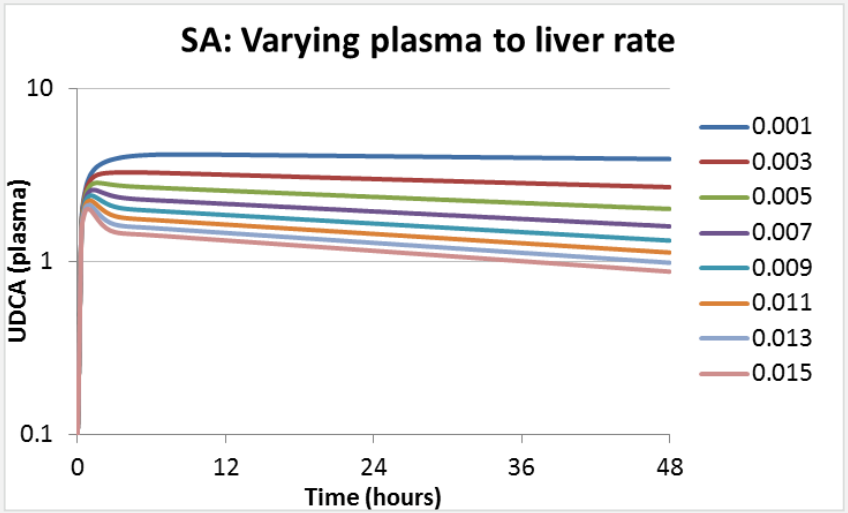


Differences between adult and child physiology

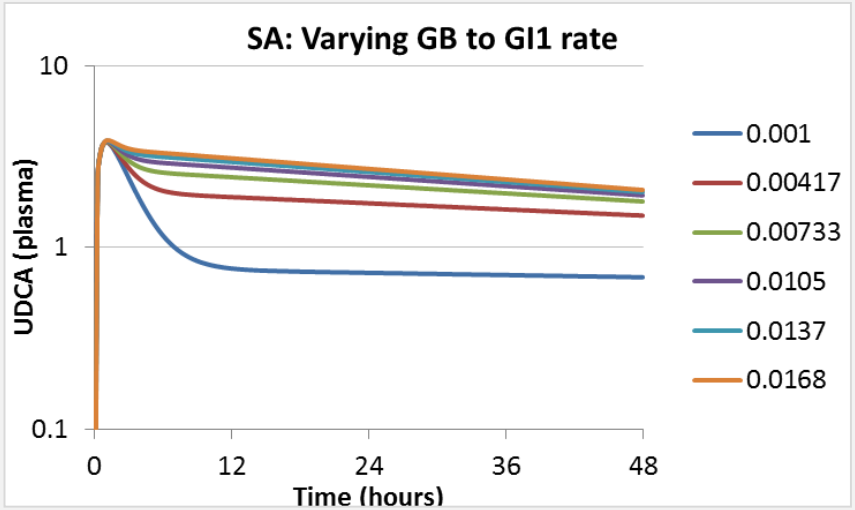
- Turn off secondary bile acid synthesis – TPN-fed neonates lack necessary intestinal bacteria

- Calibration strategy:
  1. Make an internally consistent adult model
  2. Turn off secondary bile acid synthesis to emulate neonate state
  3. Simulate ursodiol dosing, analyze *qualitative* plasma profile differences

Sensitivity analysis reveals qualitatively different effects of variability in different rate constants.

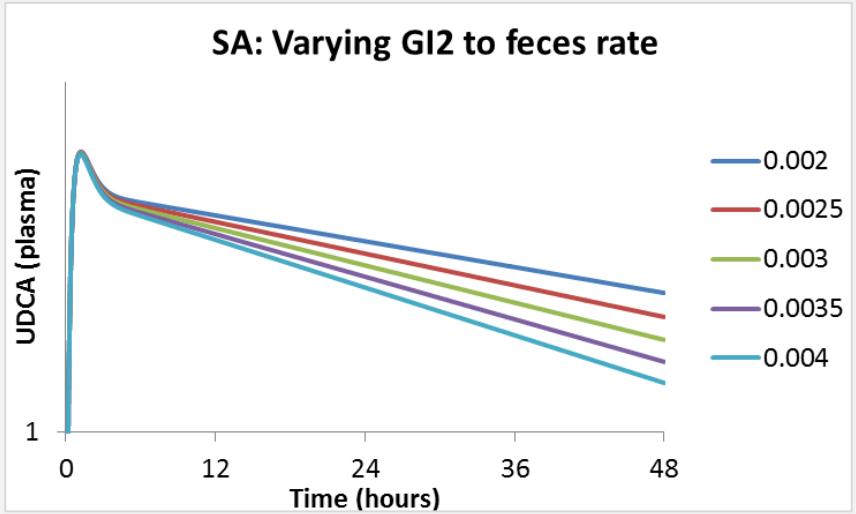


Plasma to liver rate affects Cmax, tmax, initial clearance, and terminal clearance

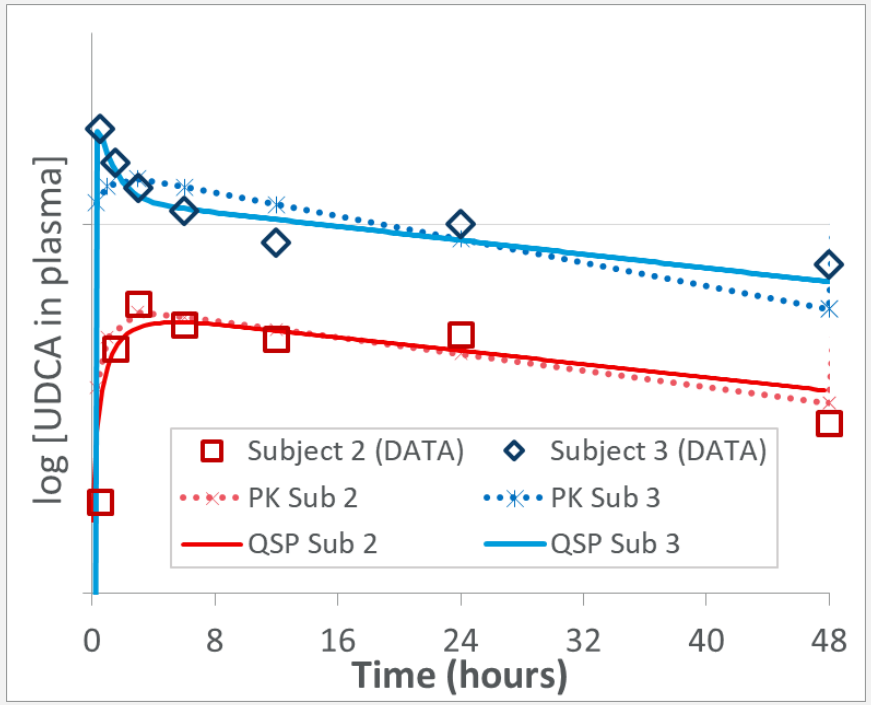


Gall bladder secretion rate affects initial and terminal clearance out of plasma

GI2 to feces rate affects terminal clearance rate only



QSP simulations capture qualitative inter-subject differences in ursodiol profiles.



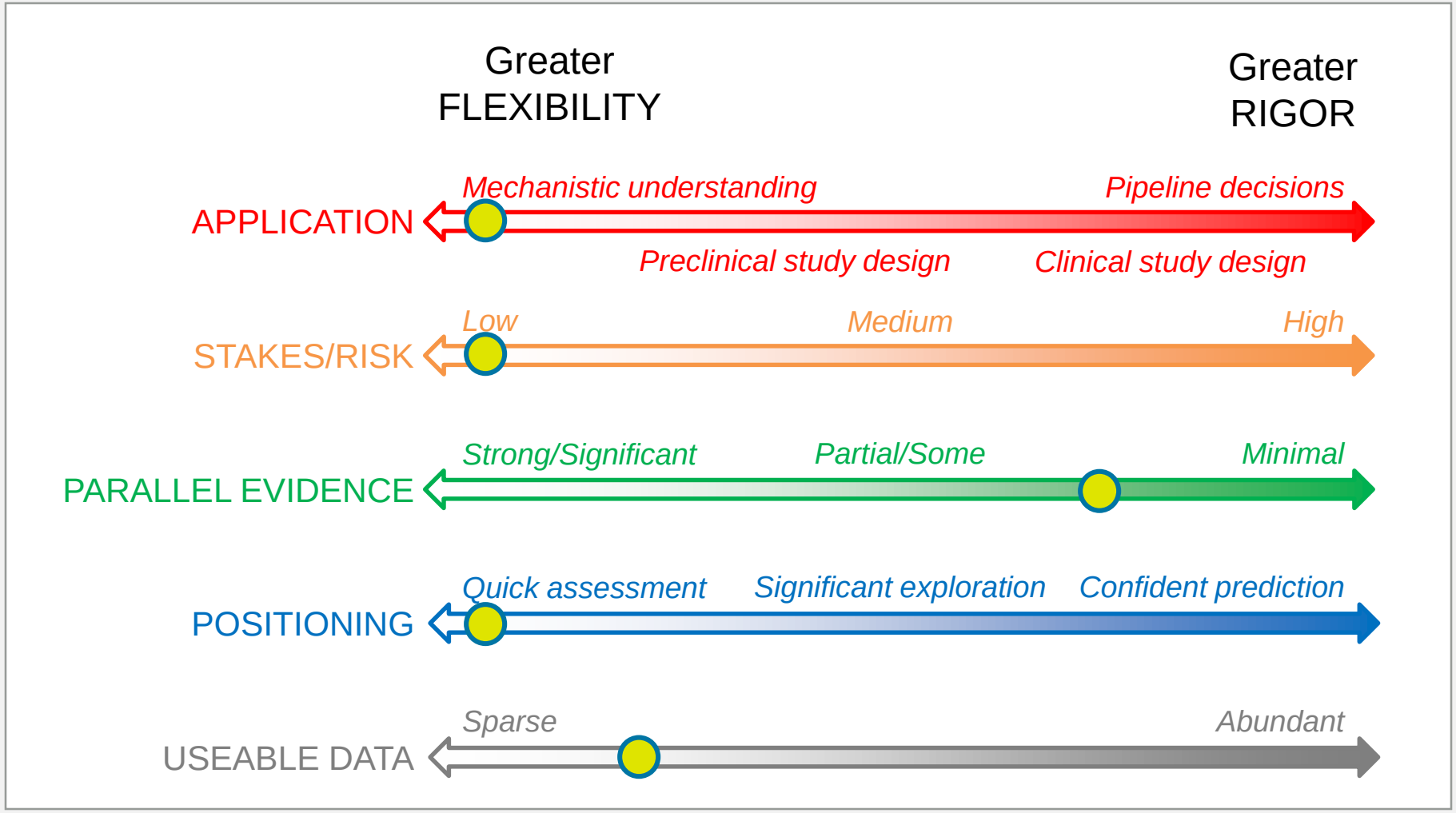
- Subject data showed qualitatively different dynamic profiles
- PK simulations do not capture these differences, QSP simulations do
- By identifying parameters that affect this profile, QSP points to likely biological sources of variability

Insights Based on Virtual Subject Analysis in the QSP Model

- Relative fluxes from GI to plasma vs. plasma to liver shape the initial peak
- Known transporter polymorphisms may explain these differences

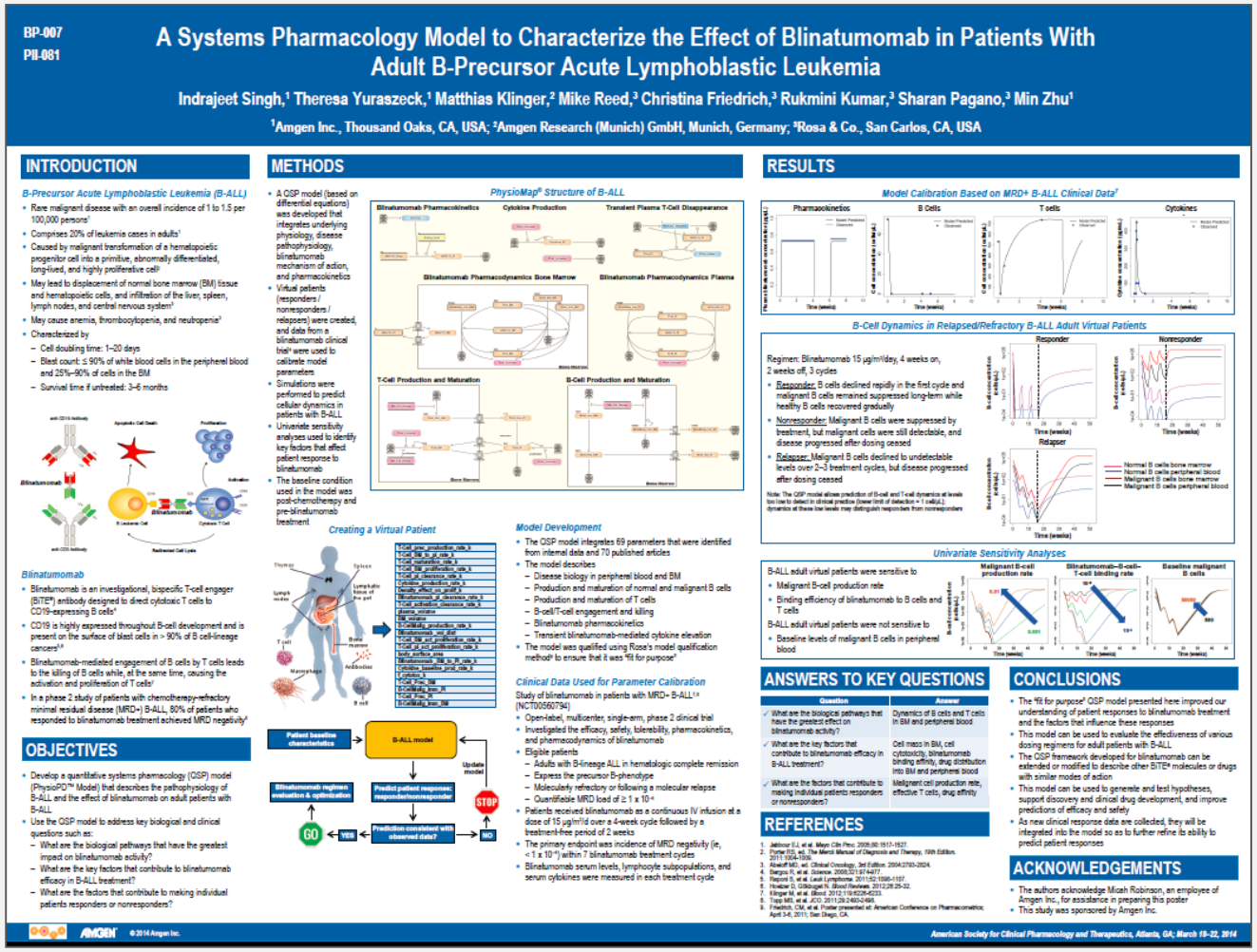
➢ QSP research made richer use of sparse data to understand neonatal biology

Where is the ursodiol QSP example positioned on the qualification context axes?



Case Example 2:
Pediatric Protocols in Immuno-Oncology

Highlights of the work for adult patients have been previously presented.



BP-007
PII-081

A Systems Pharmacology Model to Characterize the Effect of Blinatumomab in Patients With Adult B-Precursor Acute Lymphoblastic Leukemia

Indrajeet Singh,[1] Theresa Yuraszeck,[1] Matthias Klinger,[2] Mike Reed,[3] Christina Friedrich,[3] Rukmini Kumar,[3] Sharan Pagano,[3] Min Zhu[1]

[1]Amgen Inc., Thousand Oaks, CA, USA; [2]Amgen Research (Munich) GmbH, Munich, Germany; [3]Rosa & Co., San Carlos, CA, USA

INTRODUCTION

B-Precursor Acute Lymphoblastic Leukemia (B-ALL)

- Rare malignant disease with an overall incidence of 1 to 1.5 per 100,000 persons[1]
- Comprises 20% of leukemia cases in adults[1]
- Caused by malignant transformation of a hematopoietic progenitor cell into a primitive, abnormally differentiated, long-lived, and highly proliferative cell[2]
- May lead to displacement of normal bone marrow (BM) tissue and hematopoietic cells, and infiltration of the liver, spleen, lymph nodes, and central nervous system[3]
- May cause anemia, thrombocytopenia, and neutropenia[3]
- Characterized by
  - Cell doubling time: 1–20 days
  - Blast count: ≤ 90% of white blood cells in the peripheral blood and 25%–90% of cells in the BM
  - Survival time if untreated: 3–6 months

Blinatumomab

- Blinatumomab is an investigational, bispecific T-cell engager (BiTE®) antibody designed to direct cytotoxic T cells to CD19-expressing B cells[4]
- CD19 is highly expressed throughout B-cell development and is present on the surface of blast cells in > 90% of B cell-lineage cancers[5,6]
- Blinatumomab-mediated engagement of B cells by T cells leads to the killing of B cells while, at the same time, causing the activation and proliferation of T cells[7]
- In a phase 2 study of patients with chemotherapy-refractory minimal residual disease (MRD+) B-ALL, 80% of patients who responded to blinatumomab treatment achieved MRD negativity[8]

OBJECTIVES

- Develop a quantitative systems pharmacology (QSP) model (PhysioPD™ Model) that describes the pathophysiology of B-ALL and the effect of blinatumomab on adult patients with B-ALL
- Use the QSP model to address key biological and clinical questions such as:
  - What are the biological pathways that have the greatest impact on blinatumomab activity?
  - What are the key factors that contribute to blinatumomab efficacy in B-ALL treatment?
  - What are the factors that contribute to making individual patients responders or nonresponders?

METHODS

- A QSP model (based on differential equations) was developed that integrates underlying physiology, disease pathophysiology, blinatumomab mechanism of action, and pharmacokinetics
- Virtual patients (responders / nonresponders / relapsers) were created, and data from a blinatumomab clinical trial[9] were used to calibrate model parameters
- Simulations were performed to predict cellular dynamics in patients with B-ALL
- Univariate sensitivity analyses used to identify key factors that affect patient response to blinatumomab
- The baseline condition used in the model was post-chemotherapy and pre-blinatumomab treatment

PhysioMap® Structure of B-ALL

Creating a Virtual Patient

Model Development

- The QSP model integrates 69 parameters that were identified from internal data and 70 published articles
- The model describes
  - Disease biology in peripheral blood and BM
  - Production and maturation of normal and malignant B cells
  - Production and maturation of T cells
  - B-cell/T-cell engagement and killing
  - Blinatumomab pharmacokinetics
  - Transient blinatumomab-mediated cytokine elevation
- The model was qualified using Rosa's model qualification method[9] to ensure that it was "fit for purpose"[9]

Clinical Data Used for Parameter Calibration

Study of blinatumomab in patients with MRD+ B-ALL[10] (NCT00560794)

- Open-label, multicenter, single-arm, phase 2 clinical trial
- Investigated the efficacy, safety, tolerability, pharmacokinetics, and pharmacodynamics of blinatumomab
- Eligible patients
  - Adults with B-lineage ALL in hematologic complete remission
  - Express the precursor B-phenotype
  - Molecularly refractory or following a molecular relapse
  - Quantifiable MRD load of ≥ 1×10^{-4}
- Patients received blinatumomab as a continuous IV infusion at a dose of 15 µg/m²/d over a 4-week cycle followed by a treatment-free period of 2 weeks
- The primary endpoint was incidence of MRD negativity (ie, $< 1 \times 10^{-4}$) within 7 blinatumomab treatment cycles
- Blinatumomab serum levels, lymphocyte subpopulations, and serum cytokines were measured in each treatment cycle

RESULTS

Model Calibration Based on MRD+ B-ALL Clinical Data[7]

B-Cell Dynamics in Relapsed/Refractory B-ALL Adult Virtual Patients

Regimen: Blinatumomab 15 µg/m²/day, 4 weeks on, 2 weeks off, 3 cycles

- Responder: B cells declined rapidly in the first cycle and malignant B cells remained suppressed long-term while healthy B cells recovered gradually
- Nonresponder: Malignant B cells were suppressed by treatment, but malignant cells were still detectable, and disease progressed after dosing ceased
- Relapser: Malignant B cells declined to undetectable levels over 2–3 treatment cycles, but disease progressed after dosing ceased

Note: The QSP model allows prediction of B-cell and T-cell dynamics at levels too low to detect in clinical practice (lower limit of detection = 1 cell/µL); dynamics at these low levels may distinguish responders from nonresponders

Univariate Sensitivity Analyses

B-ALL adult virtual patients were sensitive to

- Malignant B-cell production rate
- Binding efficiency of blinatumomab to B cells and T cells

B-ALL adult virtual patients were not sensitive to

- Baseline levels of malignant B cells in peripheral blood

ANSWERS TO KEY QUESTIONS

Question	Answer
What are the biological pathways that have the greatest effect on blinatumomab activity?	Dynamics of B cells and T cells in BM and peripheral blood
What are the key factors that contribute to blinatumomab efficacy in B-ALL treatment?	Cell mass in BM, cell cytotoxicity, blinatumomab binding affinity, drug distribution into BM and peripheral blood
What are the factors that contribute to making individual patients responders or nonresponders?	Malignant cell production rate, effective T cells, drug affinity

CONCLUSIONS

- The "fit for purpose" QSP model presented here improved our understanding of patient responses to blinatumomab treatment and the factors that influence these responses
- This model can be used to evaluate the effectiveness of various dosing regimens for adult patients with B-ALL
- The QSP framework developed for blinatumomab can be extended or modified to describe other BiTE® molecules or drugs with similar modes of action
- This model can be used to generate and test hypotheses, support discovery and clinical drug development, and improve predictions of efficacy and safety
- As new clinical response data are collected, they will be integrated into the model so as to further refine its ability to predict patient responses

REFERENCES

1. Jabbour E.J. et al. Mayo Clin Proc. 2009;80:1517-1527.
2. Porter DS, ed. The Merck Manual of Diagnosis and Therapy. 19th Edition. 2011:1004-1009.
3. Abeloff MD, ed. Clinical Oncology. 3rd Edition. 2004:2793-2824.
4. Bargou R, et al. Science. 2008;321:974-977.
5. Raponi S, et al. Leuk Lymphoma. 2011;52:1586-1597.
6. Hoelzer D, Gökbuget N. Blood Reviews. 2012;26:25-32.
7. Klinger M, et al. Blood. 2012;119:6226-6233.
8. Topp MS, et al. JCO. 2011;29:2493-2498.
9. Friedrich, CM, et al. Poster presented at: American Conference on Pharmacometrics; April 3-6, 2011; San Diego, CA.

ACKNOWLEDGEMENTS

- The authors acknowledge Micah Robinson, an employee of Amgen Inc., for assistance in preparing this poster
- This study was sponsored by Amgen Inc.

American Society for Clinical Pharmacology and Therapeutics, Atlanta, GA; March 19-22, 2014

- Follow-on research in adults by Amgen team has also been publicly presented

Poster available for download at https://www.rosaandco.com/publications

B-Cell Acute Lymphoblastic Leukemia (B-ALL) PhysioPD™ Platform
Research supported adult and pediatric drug development.

ROSA

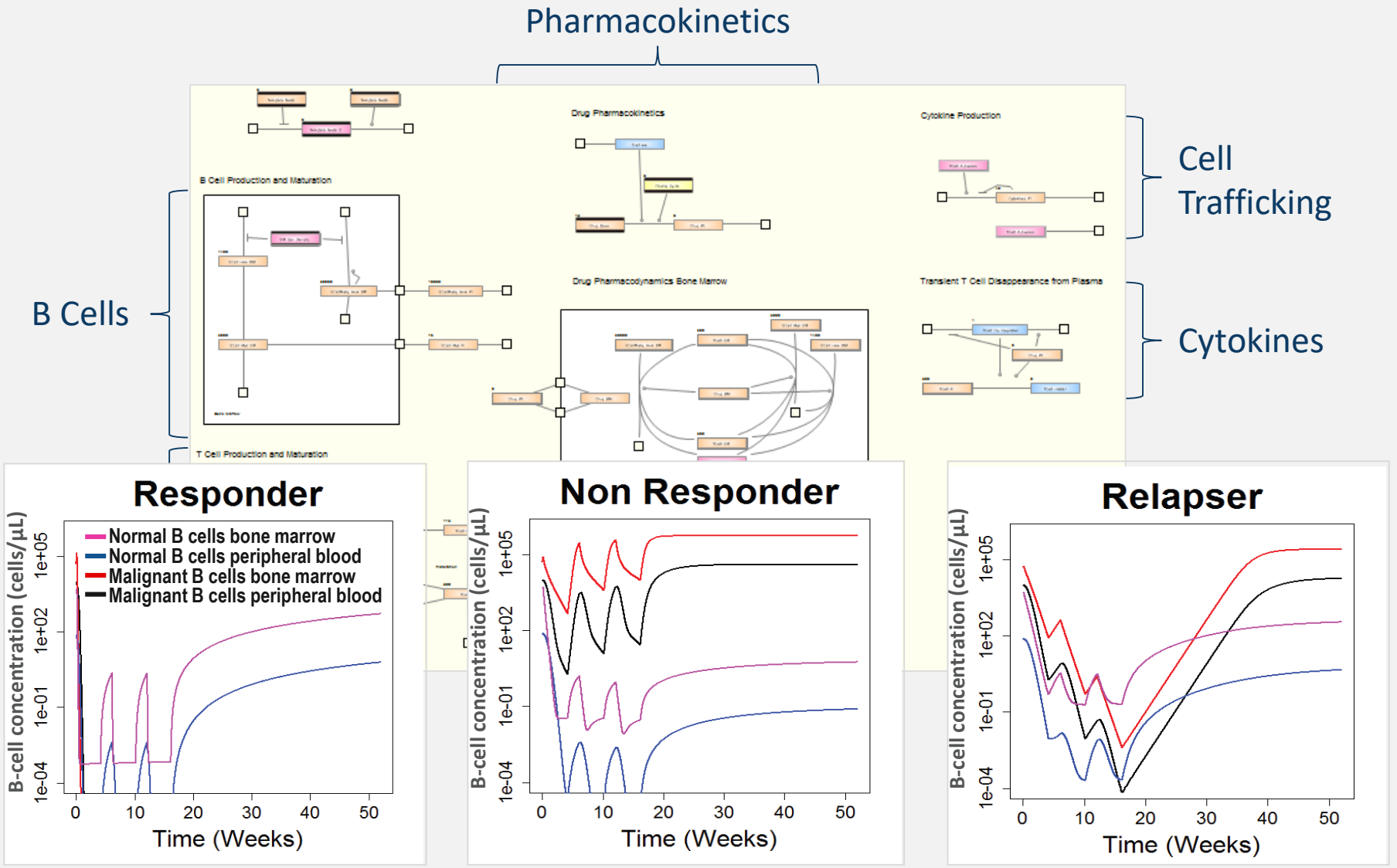
Client research challenges:

- Amgen wanted to investigate optimal dosing regimens for bispecific T-cell engager (BiTE®) antibody in adults
- Assess the similarity or difference in r/r ALL disease between adults and children

Research approach:

- Develop QSP model to represent disease progression, therapy MOA
- Create adult Virtual Patients, match Phase 2 data
- Represent known immunological and physiological differences between adults and children

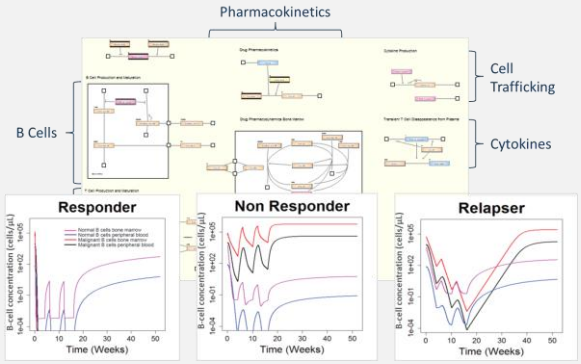
Adult B-ALL model captured responses seen in Phase 2 trial and clarified underlying mechanisms.



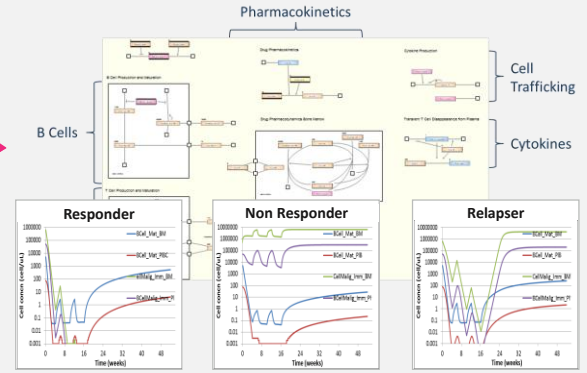
The adult QSP model provided the foundation for the pediatric model.

ROSA

Adult QSP model



Pediatric QSP model



Differences between adult and child physiology

- Literature information was used to set parameters to reflect differences between adult and child physiology/pathophysiology:
  - Bone marrow volume
  - Plasma volume
  - Body surface area
  - Cellularity of bone marrow, density effect on proliferation
  - Infant PK parameters
  - Baseline malignant B cells in bone marrow, plasma
  - Baseline T cell precursors, T cells in bone marrow and plasma
  - Malignant B cell production rate
  - B cell growth rate, death rate
  - T cell cytotoxicity
  - T cell precursor production rate, proliferation rate, clearance rate
  - Cytokine production rate

B-Cell Acute Lymphoblastic Leukemia (B-ALL)
PhysioPD™ Platform Research

ROSA

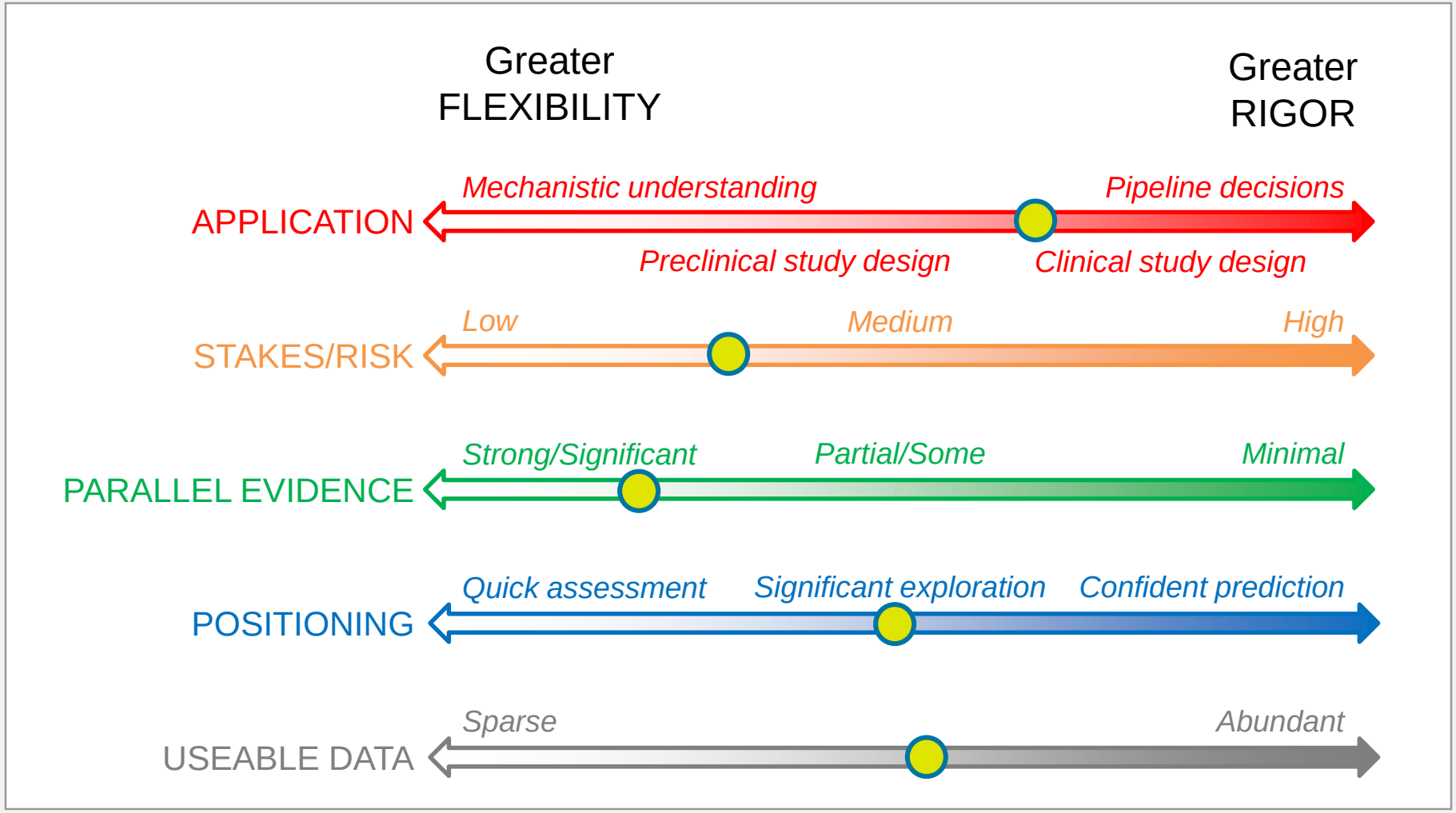
Research results:

- Clarified mechanisms of nonresponse in adults
- Confirmed that therapy was expected to be efficacious in children
- T cell population immaturity and high malignant B cell numbers may influence optimal dosing

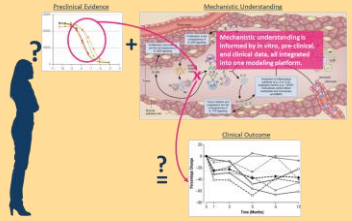
Program impact:

- Identified dosing strategies to improve likelihood of response
- Increased confidence for moving ahead in pediatric population

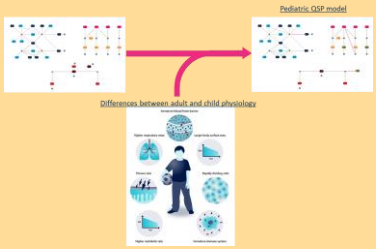
Where is the B-ALL example positioned on the qualification context axes?



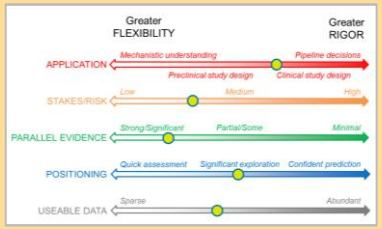
KEY TAKE-AWAYS



QSP modeling is ideally suited to get more insights out of sparse pediatric data.



A QSP model of adult physiology can serve as foundation for a pediatric model.



Not all pediatric QSP modeling is “high-risk” – qualification should be context dependent.

MODELING WITHOUT BORDERS

ACoP 10

Orlando, FL

October 20 – 23, 2019