Using Mechanistic Modeling To Support Geriatric Drug Development

Drug R&D for Adults Across the Older Age Span: A Virtual Workshop

National Academies of Sciences, Engineering, and Medicine

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Mechanistic modeling uses biological data and understanding to explore disease and drug mechanisms.

Three main sub-types of mechanistic modeling:

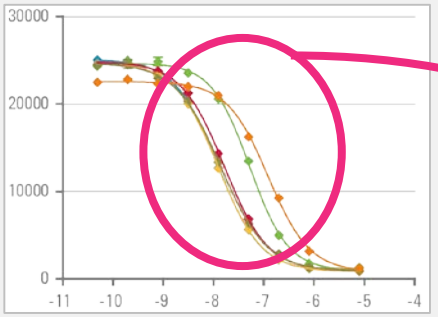
1. Quantitative Systems Pharmacology (QSP)
   - How do biological and drug mechanisms interact to produce clinical responses?
2. Quantitative Systems Toxicology (QST)
   - How do biological and drug properties interact to produce toxicities?
3. Physiologically-Based Pharmacokinetics (PBPK)
   - How do physiological properties and drug properties interact to produce exposure profiles in tissues of interest?

- While this presentation focuses on QSP, the arguments put forth apply to all mechanistic modeling approaches

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

ROSA

Preclinical Evidence



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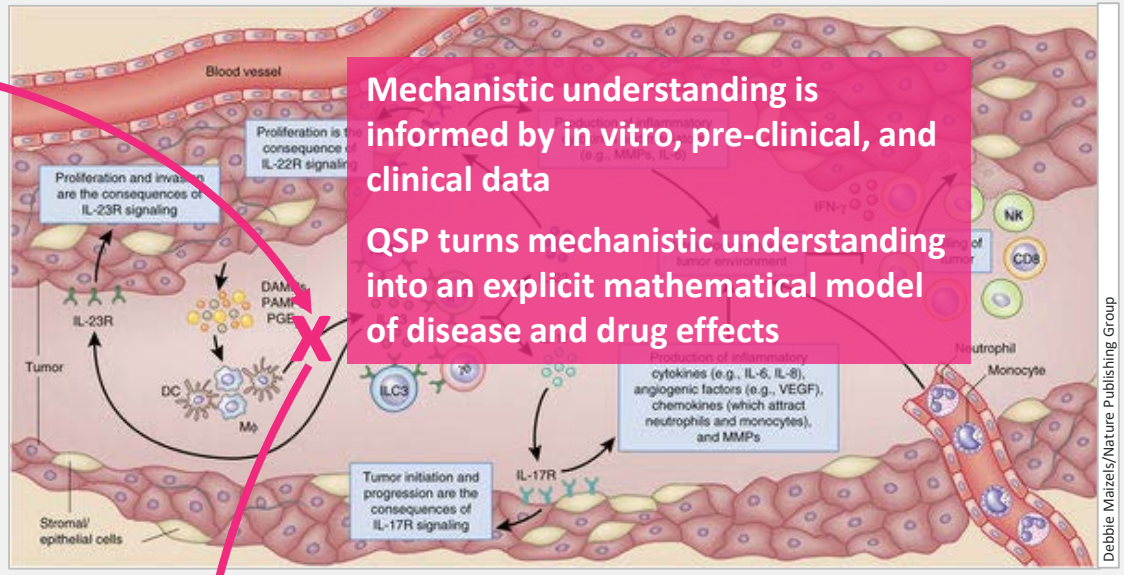
Mechanistic Understanding



Mechanistic understanding is informed by in vitro, pre-clinical, and clinical data

QSP turns mechanistic understanding into an explicit mathematical model of disease and drug effects

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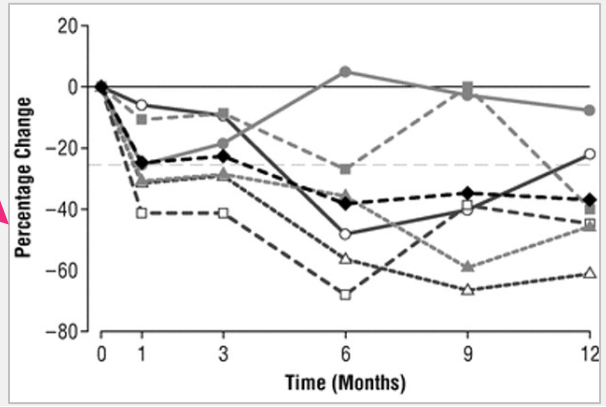
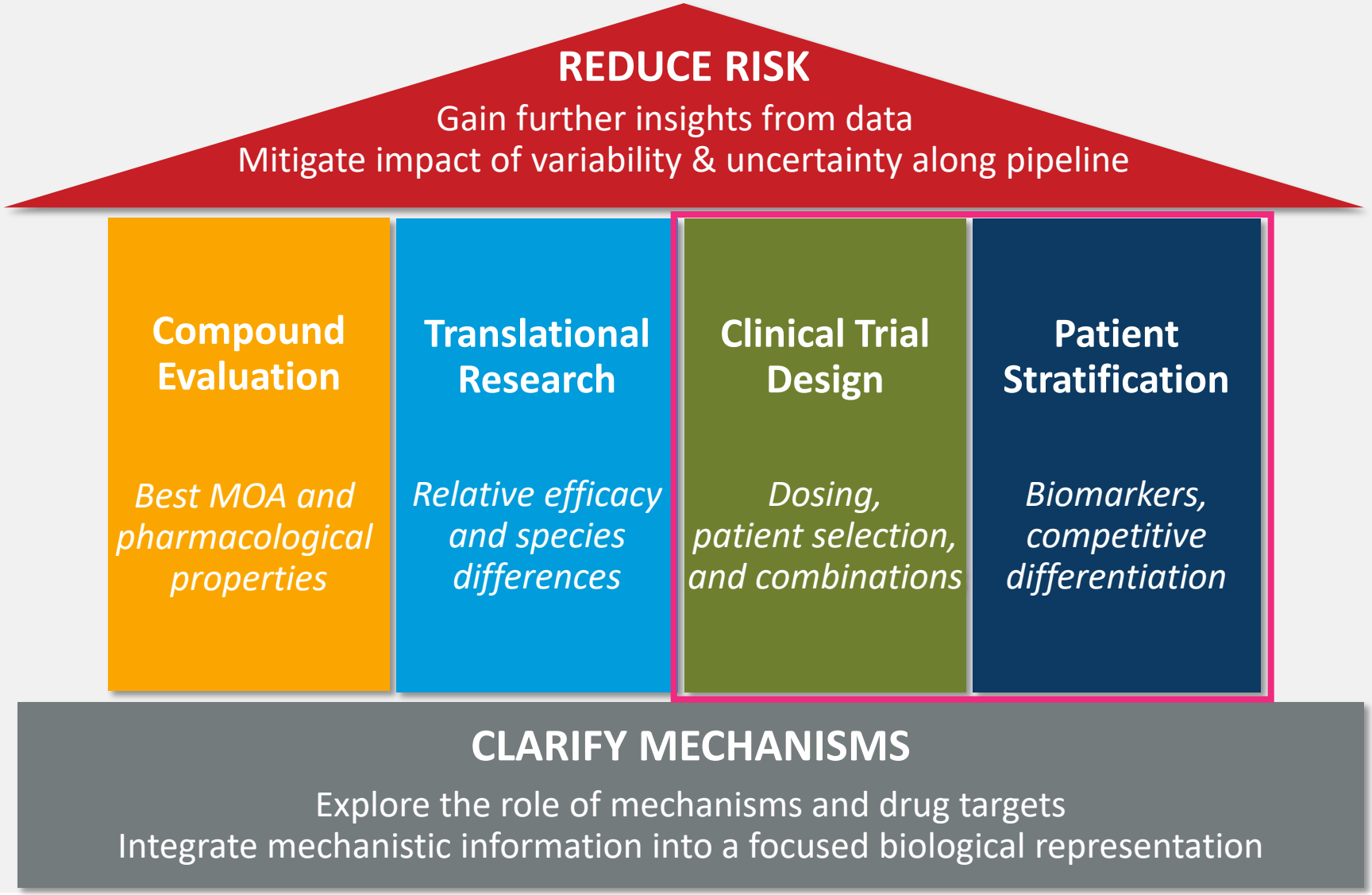
Clinical Outcome

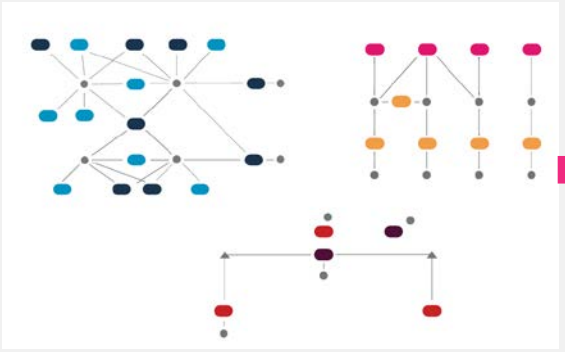


Impact of QSP Modeling: Clarifying Mechanisms Reduces Risk.

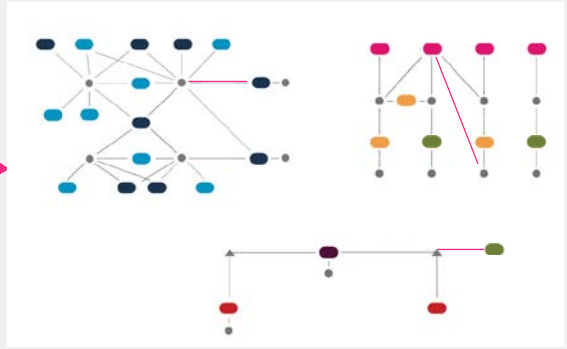


QSP modeling can inform geriatric drug development.

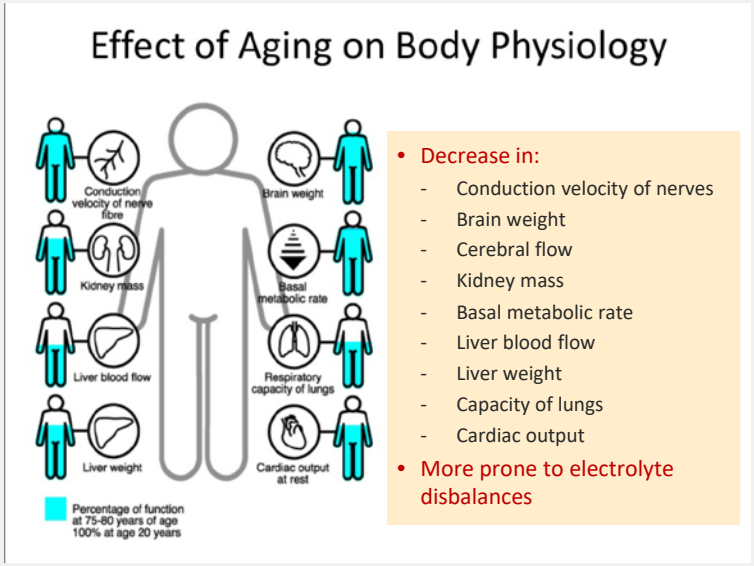
QSP model (non-geriatric adult)



Geriatric QSP model



Differences between non-geriatric and geriatric physiology



https://www.slideshare.net/Drraveesoni/psychopharmacology-in-elderly

- *Differences in drug PK and PD can result from:*
  - *Physiological effects of aging*
  - *Co-morbidities*
  - *Polypharmacy*
- *These factors can be represented mechanistically in a QSP model to better anticipate clinical outcomes*

Case Example from Pediatrics: Pediatric Protocols in Immuno-Oncology

Highlights of this work were presented as a joint Rosa/Amgen poster at 2014 ASCPT Meeting.

BP-007
PII-081

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

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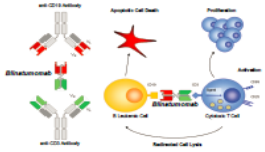
INTRODUCTION

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[2]
- 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]

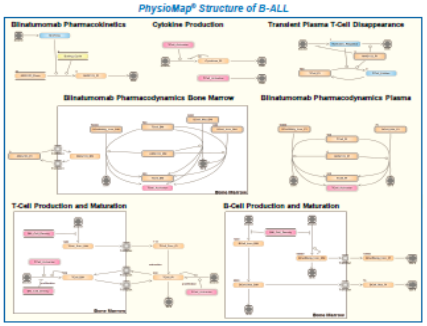
OBJECTIVES

- 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?

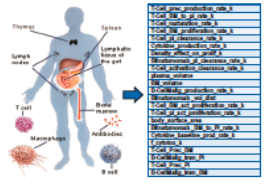
METHODS

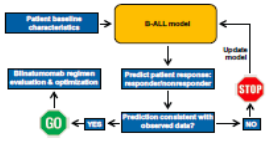
- A QSP model (based on differential equations) was developed that integrates underlying physiology, disease pathophysiology, blinatumomab mechanism of action, and pharmacokinetics
- Virtual patients (responders / nonresponders / relapsers) were created, and data from a blinatumomab clinical trial[9] 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]

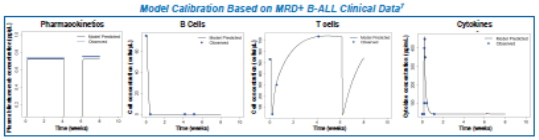
Clinical Data Used for Parameter Calibration

Study of blinatumomab in patients with MRD+ B-ALL[7,8] (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]

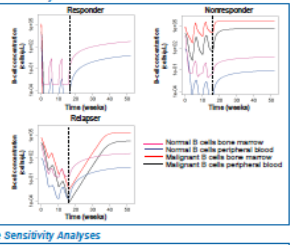


B-Cell Dynamics in Relapsed/Refractory B-ALL Adult Virtual Patients

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



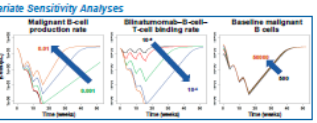
Univariate Sensitivity Analyses

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

REFERENCES

1. Jabbour E.J. et al. Mayo Clin Proc. 2009;84:1517-1527.
2. Porter RS, ed. The Merck Manual of Diagnosis and Therapy. 19th Edition. 2011:1004-1009.
3. Abeloff MD, ed. Clinical Oncology. 3rd Edition. 2004:2703-2824.
4. Bargou R, et al. Science. 2008;321:974-977.
5. Raponi S, et al. Leuk Lymphoma. 2011;52:1095-1107.
6. Howlader 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.

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

ACKNOWLEDGEMENTS

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Collaborators:

Rosa & Co

- Rukmini Kumar
- Mike Reed
- Sharan Pagano

Amgen

- Min Zhu
- Theresa Yuraszeck
- Indrajeet Singh
- Matthias Klinger

- 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

ROSA

Client Research Challenges:

- Amgen wanted to investigate optimal dosing regimens for bispecific T-cell engager (BiTE®) antibody in adults, children, and infants
- Phase 2 data in adult population were available

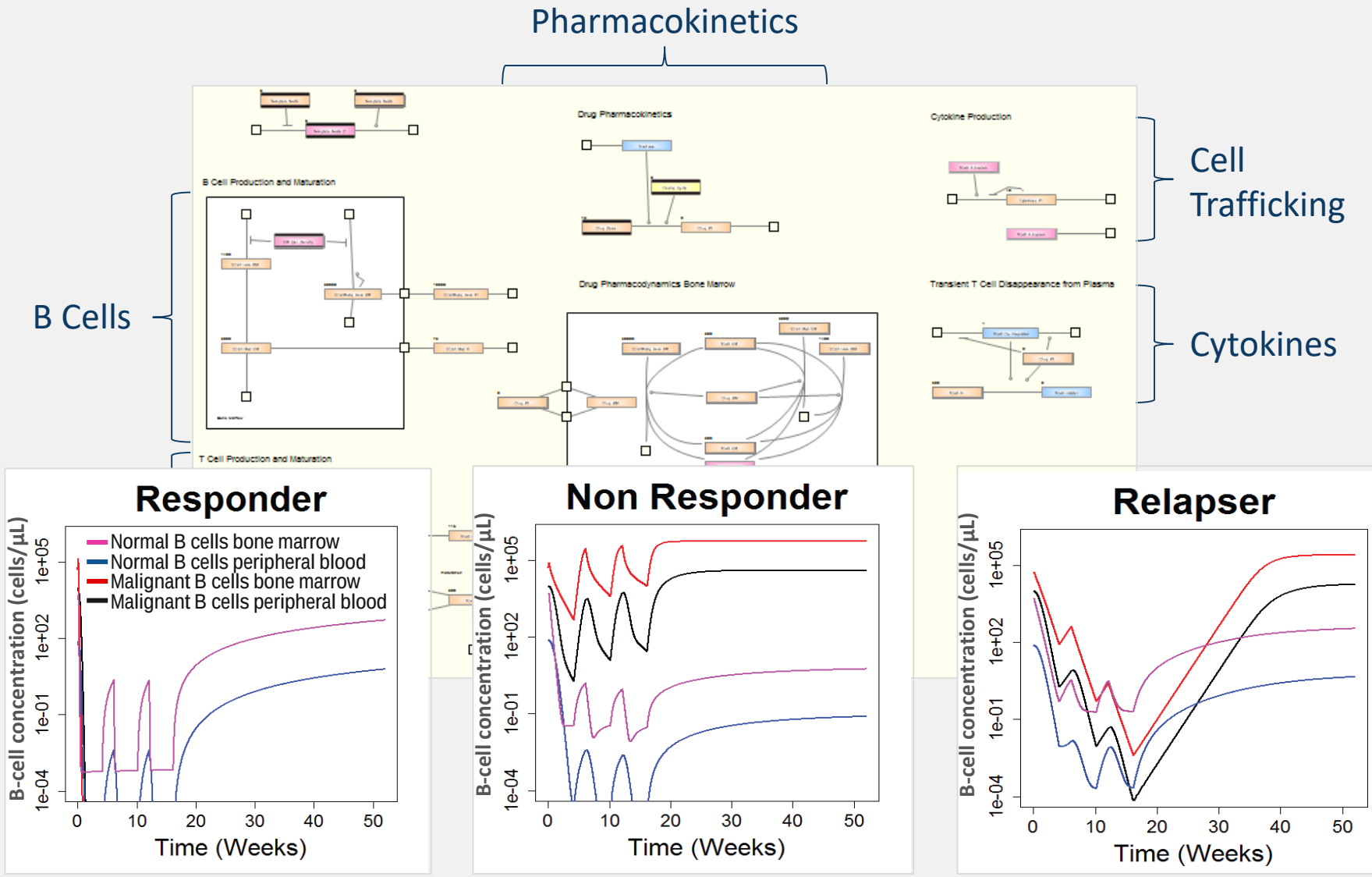
Research Approach:

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

Program Impact:

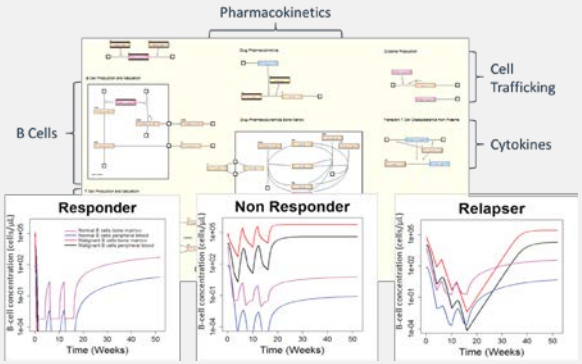
- Increased confidence for moving ahead in pediatric population
- Identified dosing strategies for all sub-populations

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

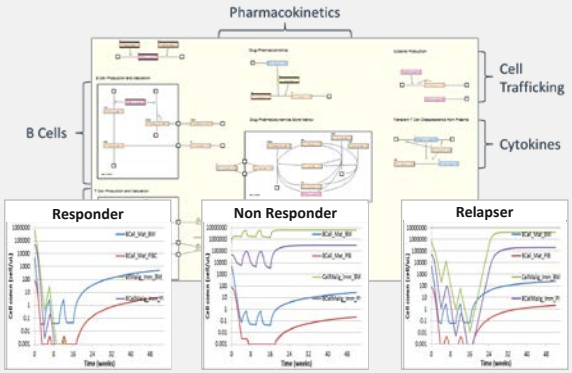


Adult QSP model served as foundation for pediatric QSP model, which was then used to refine protocols.

QSP model based on adult data



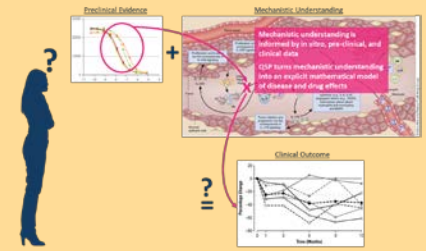
Pediatric QSP model



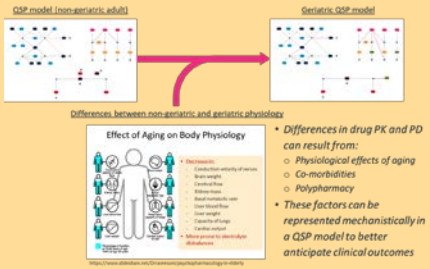
Differences between adult and child physiology

- Literature information was used to set parameters to reflect differences between adult and child/infant physiology/pathophysiology:
  - Bone marrow volume
  - Plasma volume
  - Body surface area
  - Cellularity of bone marrow, density effect on proliferation
  - Child, 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

KEY TAKE-AWAYS



QSP modeling connects the dots between mechanisms and outcomes.



A QSP model of non-geriatric adult physiology can serve as a foundation for a geriatric model.

Mechanistic impacts of aging, co-morbidities, and polypharmacy can all be incorporated.

A geriatric QSP model with a range of Virtual Patients can be used to anticipate systemic outcomes, reduce risks, and customize treatment.