
SimulationsPlus

# QSP: The Best Kept Secret for Increasing the Technical Probability of Success in Clinical Trials & Enhancing Regulatory Submissions

Lisl Shoda and Steven Chang

**19 September 2023**

# Webinar Agenda

- Brief Introduction to Simulations Plus and QSP
- Case Studies on QSP Impact in Support of Clinical Development
- Developing a QSP Standard at Simulations Plus
- Deeper Dive into QSP Capabilities in Multiple Myeloma

# Who We Are

NASDAQ: SLP

- **Cheminformatics**
  Software & Services
- **PBPK**
  Software & Services
- **Quantitative Systems Pharmacology (QSP)**
  Software & Services
- **Clinical Pharmacology & Pharmacometrics (CPP)**
  Software & Services
- **Regulatory Strategies**
  Services


**190+**

Employees Worldwide

**>25 yrs.**

Established In 1996

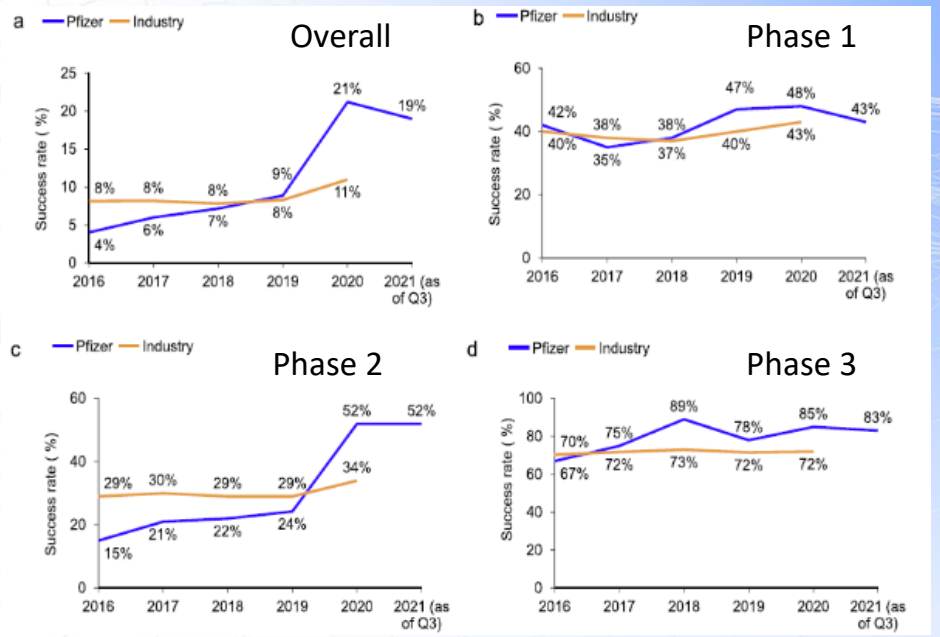
**>280** Pharmaceutical, biotechnology, chemicals, cosmetics, and consumer goods companies in the U.S., Europe, Asia, and South America

# Pharma Increasingly Adopting Modeling

## Drug development is plagued by:

- Drugs failing in clinical trials despite indications of preclinical efficacy
- Insufficient patients enrolling in trials (especially in immuno-oncology)

Pfizer moved from a 2% clinical success rate in 2010 to a 21% success rate in 2020. Their improvement was credited to focusing on “biology and quantitative decision making,” including modeling
— Fernando 2022 (PMID: 34922020)




Improved success was due to improvements in Phase 2 drug development.

QSP models integrate datasets from diverse studies, contexts, and spatiotemporal scales into a mathematical framework that reflects our knowledge of the system…. These models exploit this integrated, mechanistic representation to predict outcomes in untested scenarios, prioritizing relevant biological detail over identifiability..”

**The utility of QSP models…; Musante, C. J. 2017**

# QSP Submissions to FDA are Accelerating & Attracting Attention

157 Submissions Containing QSP as of Dec 2020

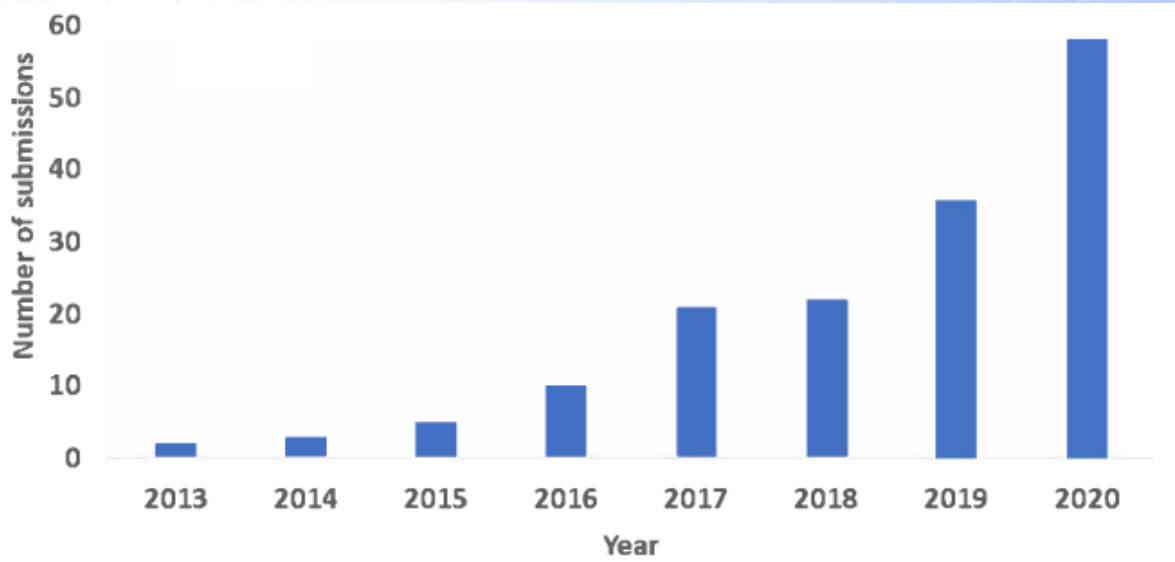
**2013**
- 1st FDA Submission in 2013 Pre-IND in Oncology

**2014**
- rH parathyroid hormone QSP Model applied in NDA review to support dose selection

**2019**
- ASCPT Workshop Recognizes Increased Regulatory Discussion & Identifies potential for question-based/fit-for-purpose validation

**2020**
- FDA hosts Scientific Exchange with Industry on when & how to approach standards for model validation

**2023**
- FDA Workshop on creating a roadmap for QSP-informed rare disease drug development




Bai 2021 [PMID 34734497]

# Leveraging QSP to Impact Drug Development Programs

## Trial Design

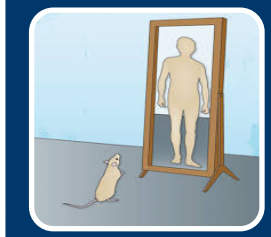
- Contributed to the trial design of over **40 large scale clinical trials**
- Simulation analysis sufficiently compelling to FDA to **forego a Phase III trial arm**

## Drug Mechanism of Action or Toxicity

- Helped prove drug mechanism hypotheses which led FDA to **change a drug label**
- Identified mechanisms of toxicity for over 25 compounds submitted or intended for regulatory agencies
- Identified mechanisms of action in support of ongoing clinical development

## Identify Patient Response Groups

- **Identified non-responders** to drug who were predisposed to a poor response- stratified by genetic and independent factors
- Integration of RWD, ultimately to develop an algorithm **identifying patients at higher risk** for DILI



## Predicted Phase I and II Responses

- Successfully **predicted first-in-human efficacy** failures based on successful preclinical results
- Successfully **predicted first-in-human efficacy** successes based on successful preclinical results
- Successfully **predicted Phase 2 failures** based on insufficient efficacy

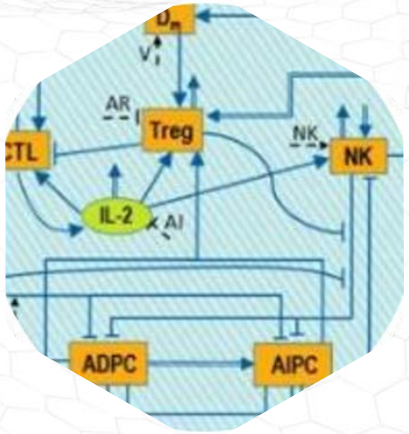
## Predicted Phase III Trial Results

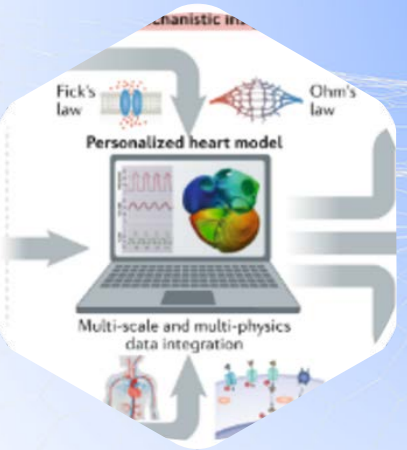
- Correct positive and negative results across several disease states using our models
- Successfully **predicted Phase III failures**, even when Phase II showed statistically significant improvement in clinical endpoints
- Successfully **predicted safe doses** for phase III trials

## MIDD / Regulatory Interactions

- Simulation analysis supported **removal of clinical hold** related to liver safety signals; subsequent phase III clinical trials with no reported liver safety signals
- Simulations performed to **obviate clinical studies** needed to address FDA's Fixed Combination Rule

# QSP is the Mechanistic Representation of Health and Disease to Predict Drug Efficacy and Safety


### Fit-for-Purpose Models

- Model that generates the required results to the necessary level of accuracy within a manageable amount of time, i.e., it achieves its computational aim at a reasonable computational expense

### Platform Models

- Interplay of multiple drugs, pathways, tissues
- Representation of healthy disease & comparisons to standards of care
- Mechanistically link target modulation of biomarkers to changes in outcomes
- Reused, adapted, and repurposed

### Disease Progression Models

- Build upon platform models
- Simultaneously support/fit as many drugs as possible
- Simulate patients from disease diagnosis → standard of care → multiple drugs of interest

"QSP models integrate datasets from diverse studies, contexts, and spatiotemporal scales into a mathematical framework that reflects our knowledge of the system. These models exploit this integrated, mechanistic representation to predict outcomes in untested scenarios, prioritizing relevant biological detail over identifiability."

**Musante, C. J., et al. 2017**

# Simulations Plus Has A Library of Existing QSP and QST Models to Address Your Questions

## QSP: Inflammatory and Fibrotic Diseases

- Non-alcoholic fatty liver disease / steatohepatitis (NAFLD/NASH)
- Idiopathic pulmonary fibrosis (IPF)
- Interstitial lung disease (ILD) associated with systemic sclerosis
- Wound healing after myocardial infarction (MI)
- Uric acid disposition in gout
- Dysregulation of alternative and terminal pathways (AP, TP) of complement

## QST: Liver and Kidney Safety

- Drug induced liver injury (DILI)
- Drug induced acute kidney injury

## QSP: Immuno-Oncology

- Acute myeloid leukemia (AML)
- Multiple myeloma (MM)
- Solid tumor (NSCLC, melanoma)
- Diffuse large B-cell lymphoma (DLBCL)

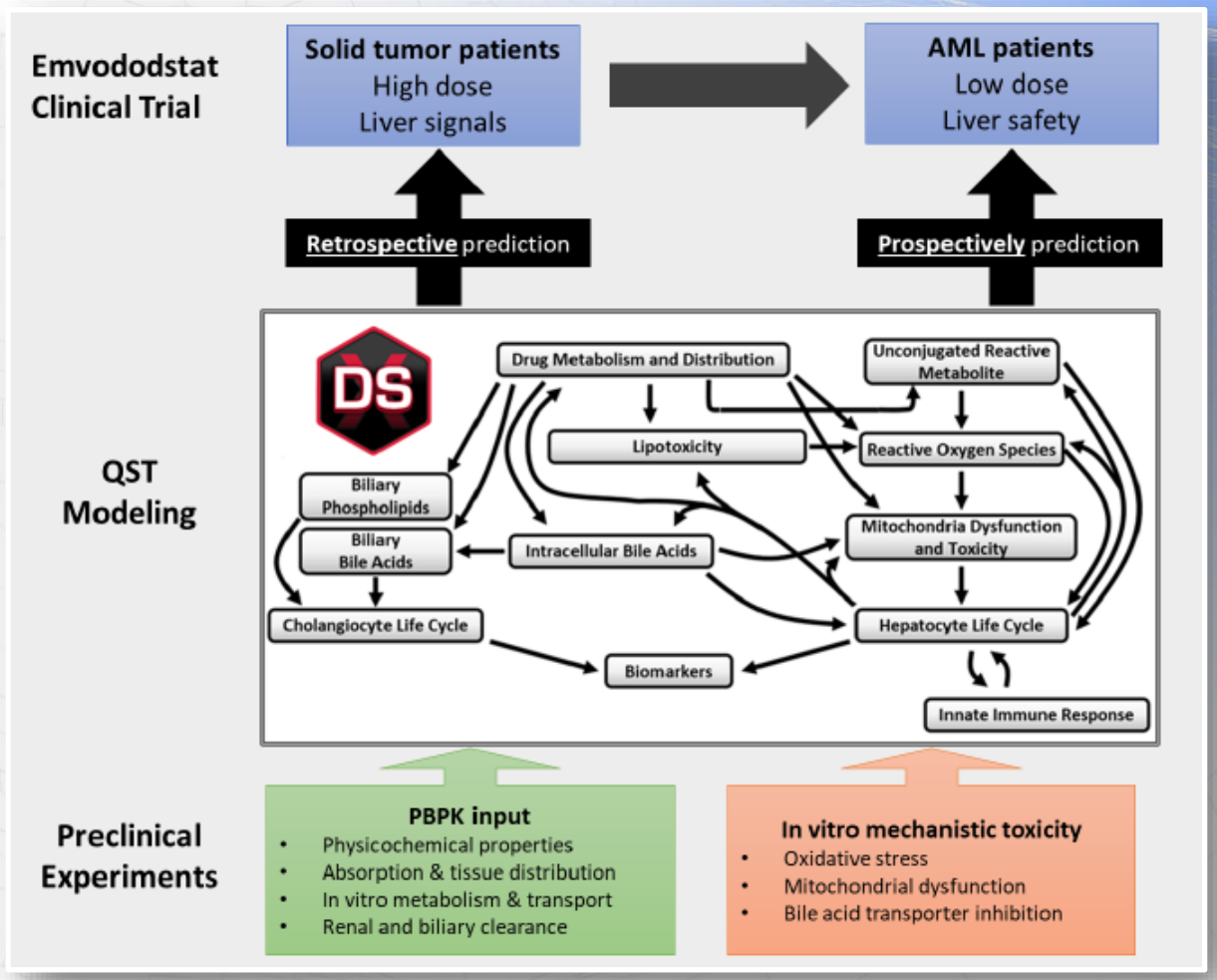
## QSP: Autoimmune Diseases

- Rheumatoid arthritis (RA)
- Psoriatic arthritis (PSA)
- Psoriasis (PSO)
- Atopic dermatitis (AD)
- Systemic lupus erythematosus (SLE)
- Ulcerative colitis (UC)
- Crohn's disease (CD)

***And the library of models is growing!!***

# Case Study: QST Informed Safe Dose Selection of Emvododstat in Acute Myeloid Leukemia (AML) Patients

- Emvodostat for the treatment of solid tumors initially terminated after two patients experienced drug-induced liver failure
- Potential for AML efficacy using lower dosing regimens
- Application of DILIsym to predict liver safety for lower doses
  - Retrospective simulations to reproduce observed hepatotoxicity
  - Prospective simulations to predict liver safety with proposed dosing

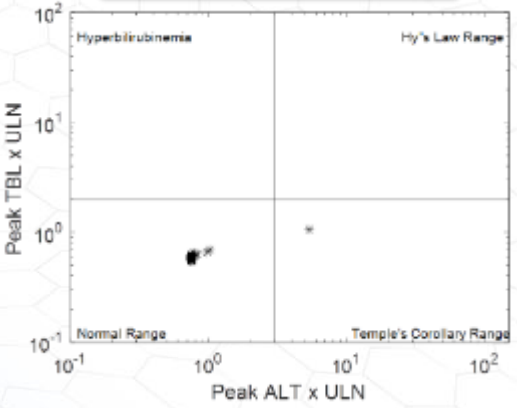



*ASCPT 2023*

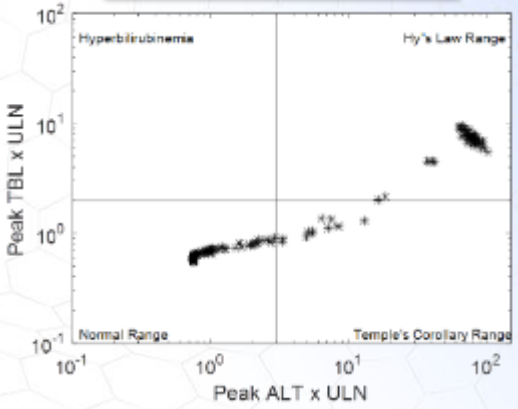
# DILIsym Retrospectively Reproduced Observed Liver Safety Signals and Prospectively Predicted Safety with Alternate Regimens

- PBPK model-informed liver exposure to emvododstat and its metabolite
- Exposure-dependent effects on bile acid transporters, mitochondrial function, and oxidative stress
- Simulation of historic clinical protocols demonstrated dose-dependent hepatotoxicity
- **No hepatotoxicity was predicted for prospective dose regimens**

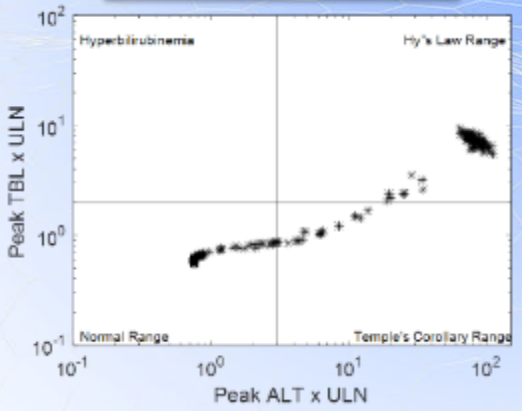
100 mg BID 16 wk



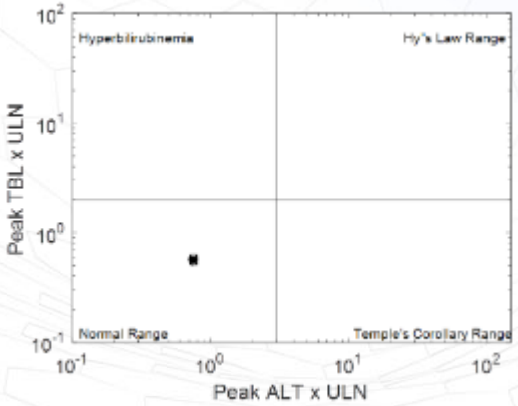

160 mg BID 16 wk



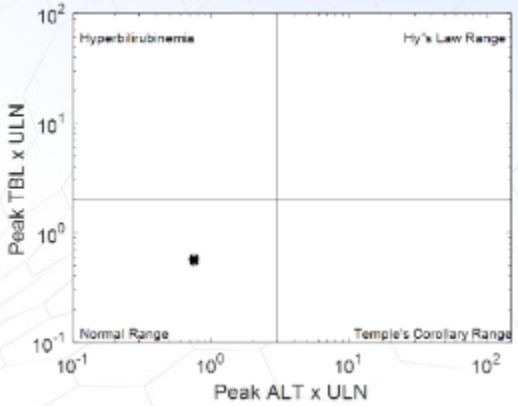

200 mg BID 16 wk




40mg/20mg BID 32 wk




80mg/40mg BID 32 wk




**No clinical stop protocol**

# Prospective DILIsym Simulations of Emvododstat Validated with Recent Clinical Trial Results

- **PK exposure and liver safety outcomes from recent clinical trials of Emvododstat are consistent with simulation results, validating DILIsym predictions**
  - Among 33 patients who participated in the AML clinical trial (PTC299-HEM-001-LEU), only 5 patients experienced elevations in AST/ALT, all of which were mild (Grade 1), all resolving within a short period of time and no patient showed symptoms of hepatic toxicity

# Case Study: QSP Identification of Key Mechanism of Action Underpinning Efficacy for FGFR1/KLB Agonists

- FGF21 analogs, acting as FGFR1/β-Klotho agonists, are in development to treat metabolic diseases
  - Promising in preclinical studies
  - Variable efficacy in clinical trials
- Representation of multiple FGF21 analogs in NAFLDsym to better understand the mechanistic underpinnings driving clinical efficacy

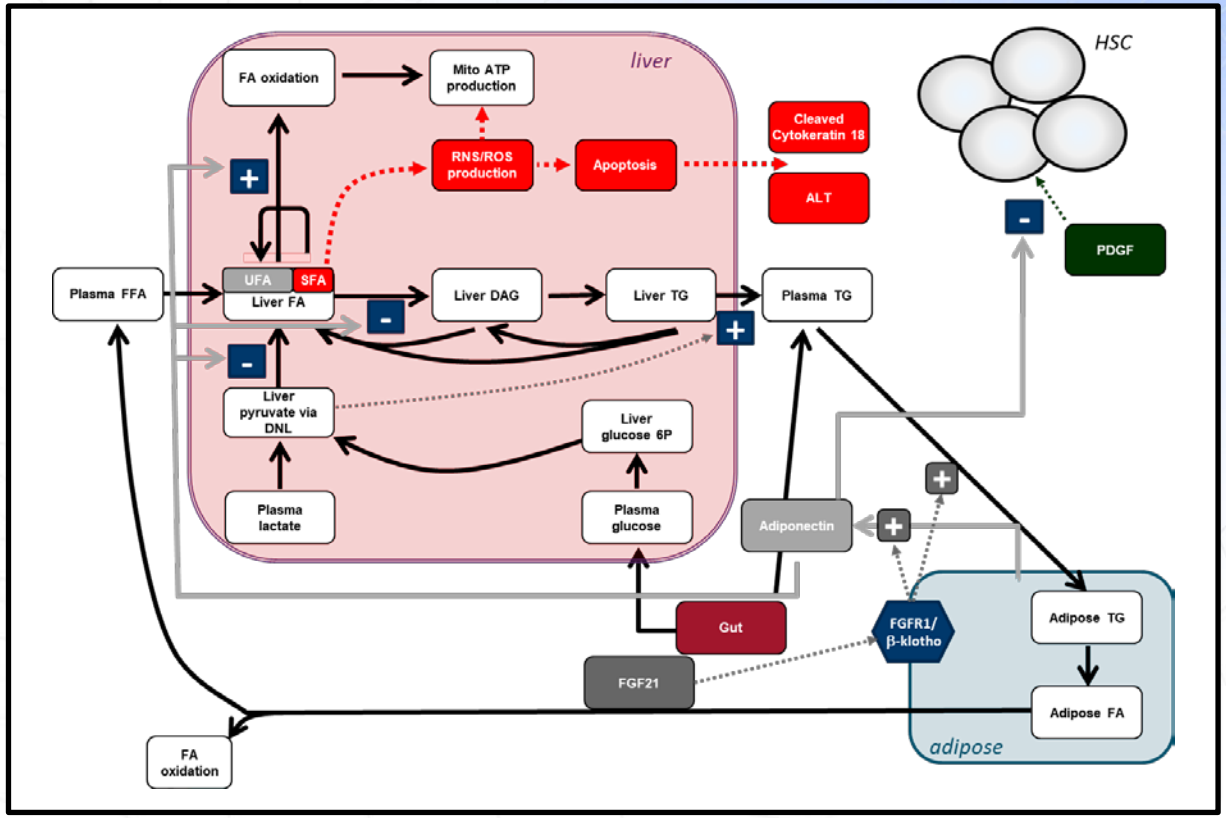
| Tissue | FGF21 Effects (FGFR1 agonist) |
|---|---|
| Adipose | FGF21 effects on adiponectin production |
| | Km adipose adiponectin attenuation (*in SimPops*) |
| Liver | Adiponectin inhibition of liver DNL |
| | Adiponectin inhibition of liver MGAT |
| | Adiponectin inhibition of liver VLDL-TG secretion |

**Greater efficacy predicted for FGFR1/beta-klotho receptor agonists that achieve 60% or greater increases in serum adiponectin**

Vinal Lakhani[1], Giridhar Tirucherai[2], Grant Generaux[1], Scott Q Siler[1]
[1]DILIsym Services Division, Simulations Plus Inc., Research Triangle Park, NC
[2]Bristol-Myers Squibb, Princeton, NJ
CONTACT INFORMATION: vinal.lakhani@simulations-plus.com

Bristol Myers Squibb
SimulationsPlus

*The Liver Meeting 2022*





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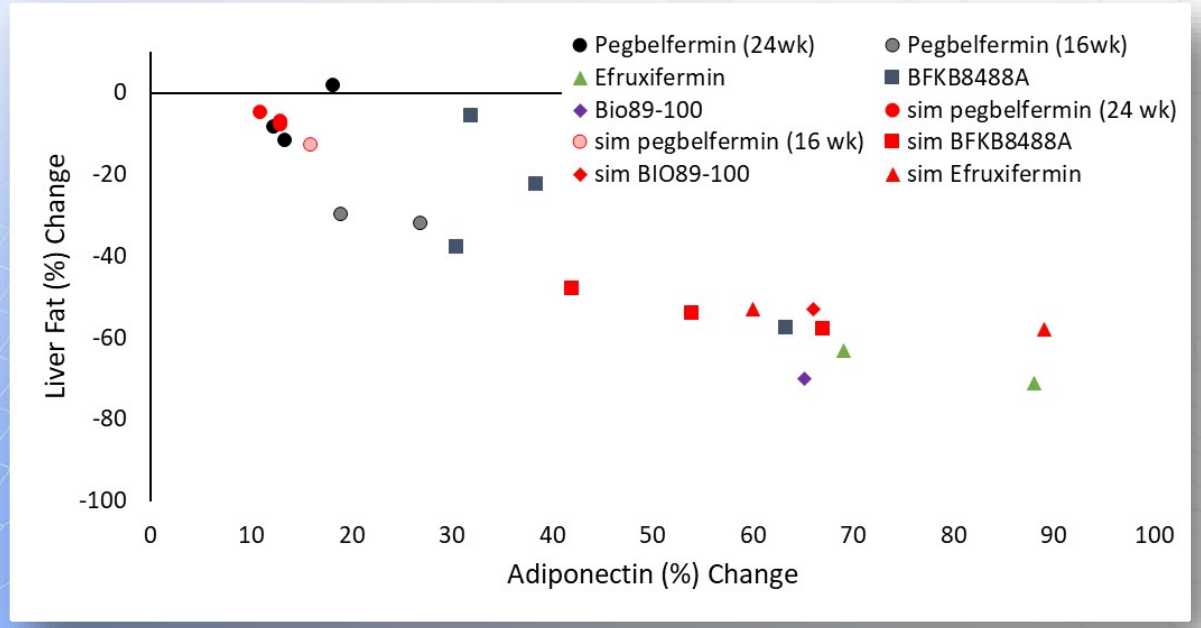
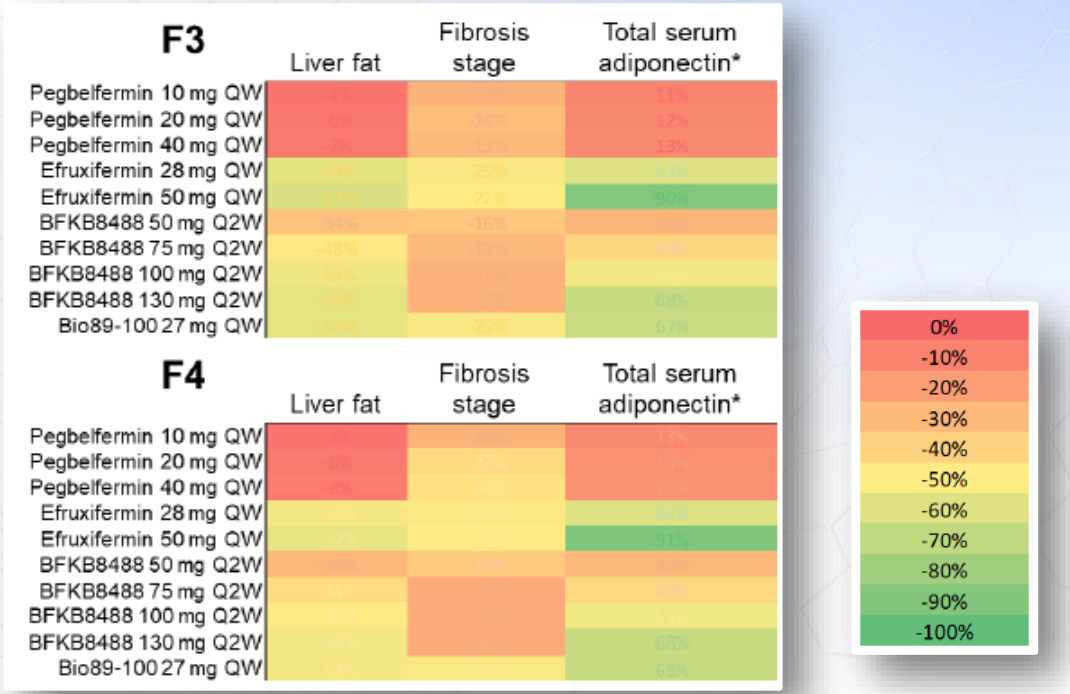
# NAFLDsym Predicted Association of Clinical Efficacy with Increased Adiponectin

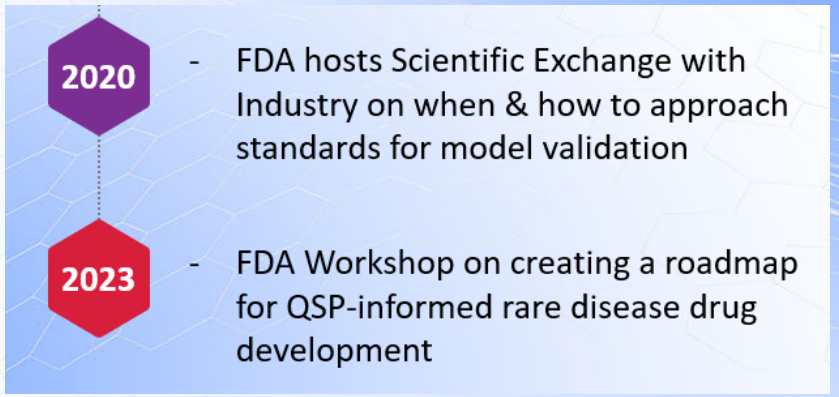
- Head-to-head comparison of four FGF21 analogs using NAFLDsym
  - Integration of compound exposure and effects of FGF21 analogs in simulated patients matched to clinical trials
- Reproduction of relationship between increased adiponectin and decreased liver fat
- Predicted efficacy aligns with potency of adiponectin effect

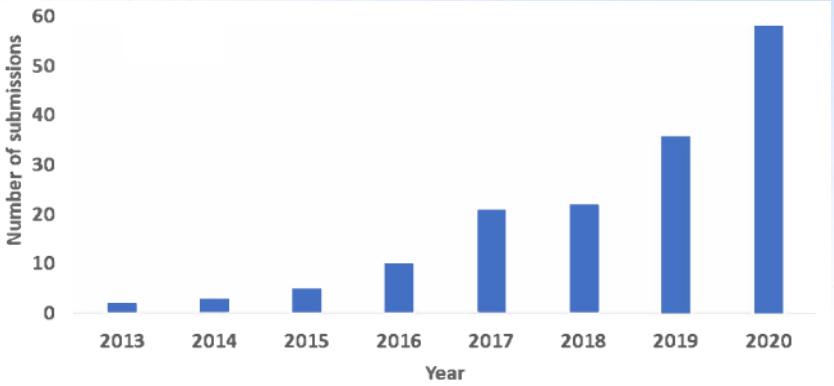


# All Agree QSP Needs Standardization

- Regulatory agencies see increasing number of submissions with QSP
  - Currently, these are bespoke built-for-purpose models using a diversity of languages, modeling platforms, techniques…
  - The ability to assess and understanding the models within the Briefing doc response window (30-60 days) is a difficult challenge
- Pharma including QSP in their submissions are also left making a best guess as to what will be required by regulatory agencies
- QSP standardization previously unsuccessful through consortium discussions



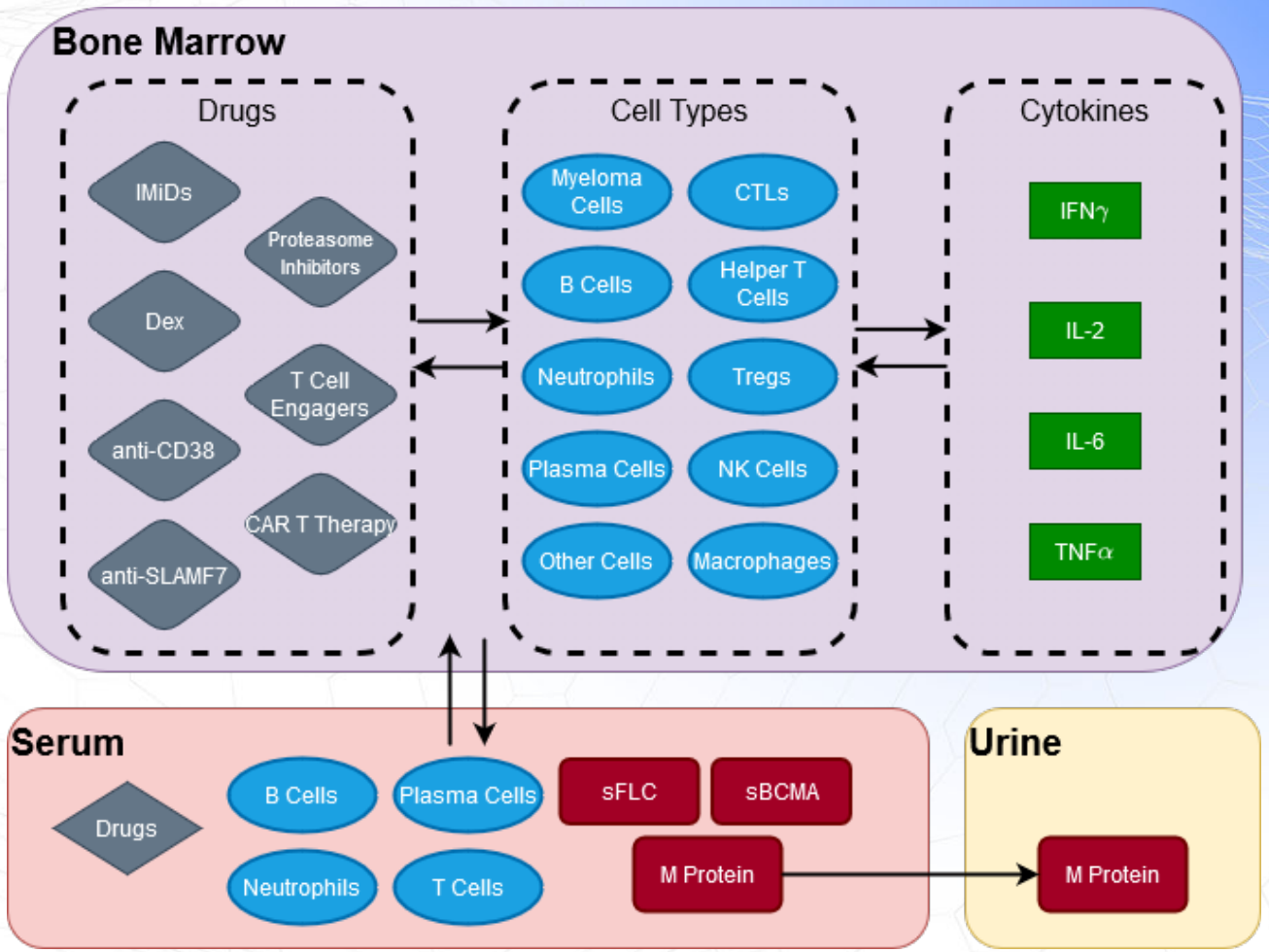



# SLP Introducing QSP Standardization

- SLP will have a QSP standard available for its customers
  - Model implementation and extension
  - Virtual populations simultaneously fit to all relevant phase 2/3 drug trials
  - Consistent approach to model fitting and validation
- Within these standards, the broader clinical community can be educated on what these models can do and how to trust the model outputs
- These levels of standardization would make it easier on both sides (Regulatory and Pharma) to operate within a familiar environment

# Overview of Multiple Myeloma QSP Model

- The model represents the critical biological elements of MM disease biology and drug mechanisms of action
  - Disease biology: MM cells, MM-produced biomarkers (M protein, sFLC, sBCMA), immune cells (CTL, Th, Tregs, Macs, NK cells), and cytokines (IL-2, IL-6, IFN-γ, TNF-α)
  - Model utilizes clinical biomarkers and cell counts to generate clinical endpoints
- Over 30 phase 2/3 clinical trials are used in training this model, spanning over 25 drug regimens and 14 distinct therapeutic agents
  - Drug MoAs: proteasome inhibitors, IMiDs, CELMoDs, dexamethasone, mAbs, cell engagers, CART T cell therapies
  - Fitting the same disease model to many therapies simultaneously helps to calibrate core disease and drug specific MoAs
  - # of clinical endpoints…
- Resulting in a group of virtual MM patients that is representative of the real MM patients that enroll in actual drug trials

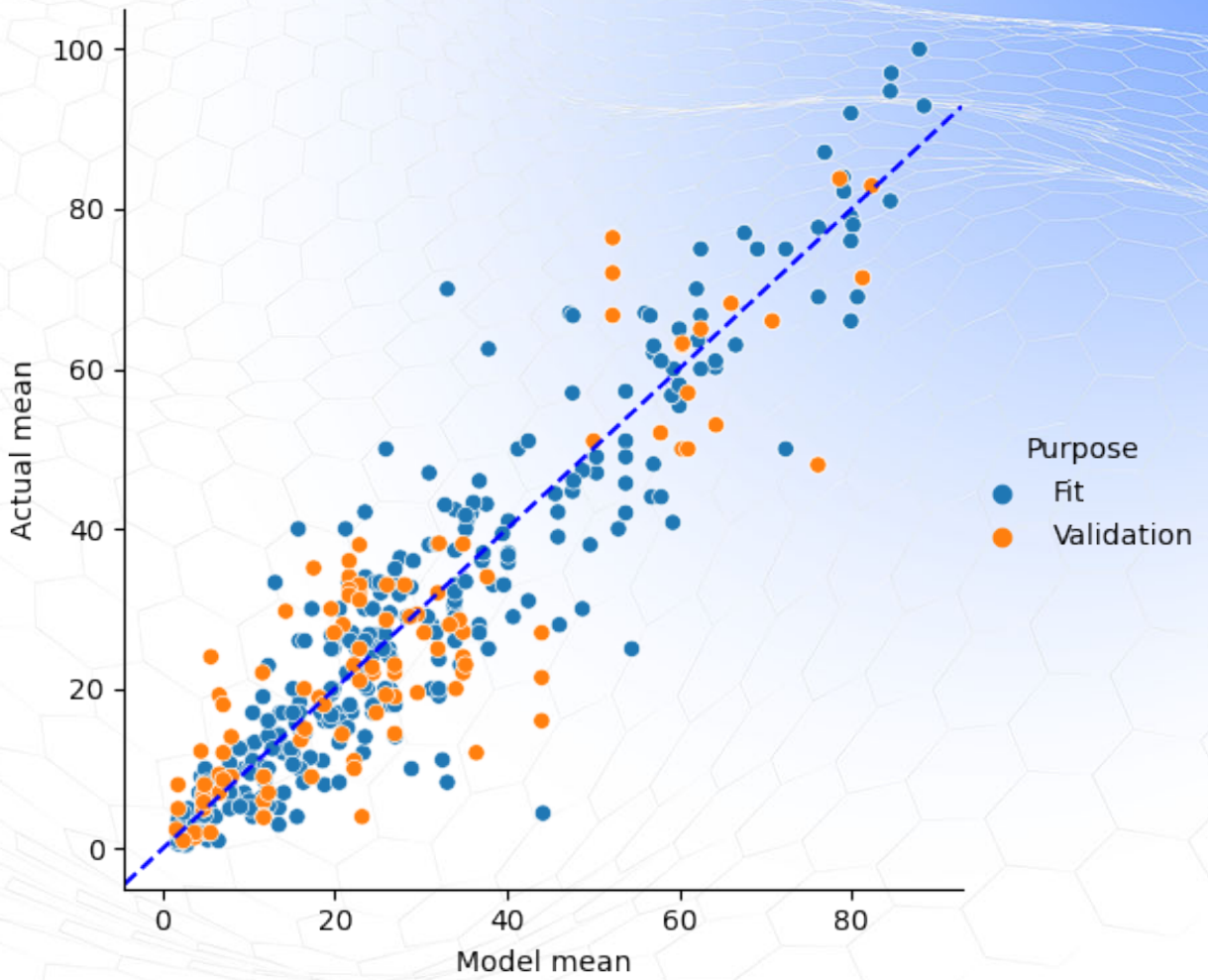


# Standard for Assessing Model Fitness

- In addition to a model's "score" (used during optimization), we employ an alternative measure of model quality termed "coverage" that is independent of the training process
- Coverage is the percentage of data inside the model's 90% confidence interval
  - The Confidence Interval is our model's estimate of the range of trial means that repeated trials would yield
  - By definition, we expect 90% of the data should be inside the 90% confidence interval (not 100%)
  - More practically, a QSP model that performs well is likely closer to 70% coverage due to various factors including, but not limited to:
    - Subtle differences in trial populations used for training
    - Differences in how clinicians measure disease (especially for diseases with standards of care that rapidly change)
    - Other sources of noise and real world variability
- Coverage can be assessed across virtual populations and models and is thus a useful comparator for ever-evolving models.

# Overall Quality of Fit

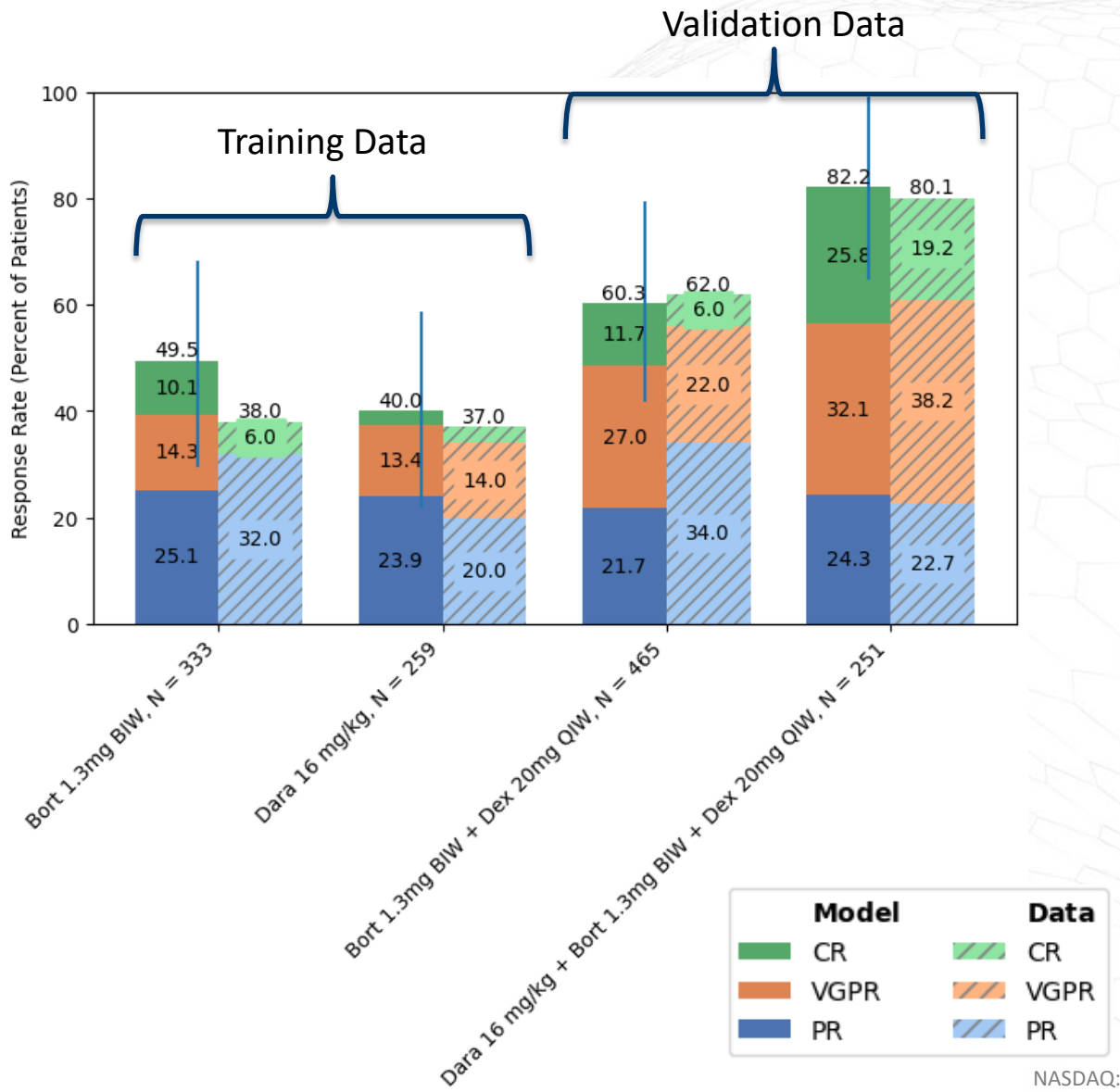
- The parity plot shown here highlights quality of fit across all response endpoints in the myeloma model
  - Fit indicates the data was used in VPop optimization (569 clinical trial mean values)
  - Validation indicates the data was held out (194 clinical trial mean values)



# Model Successfully Predicts Tal + Dara Efficacy

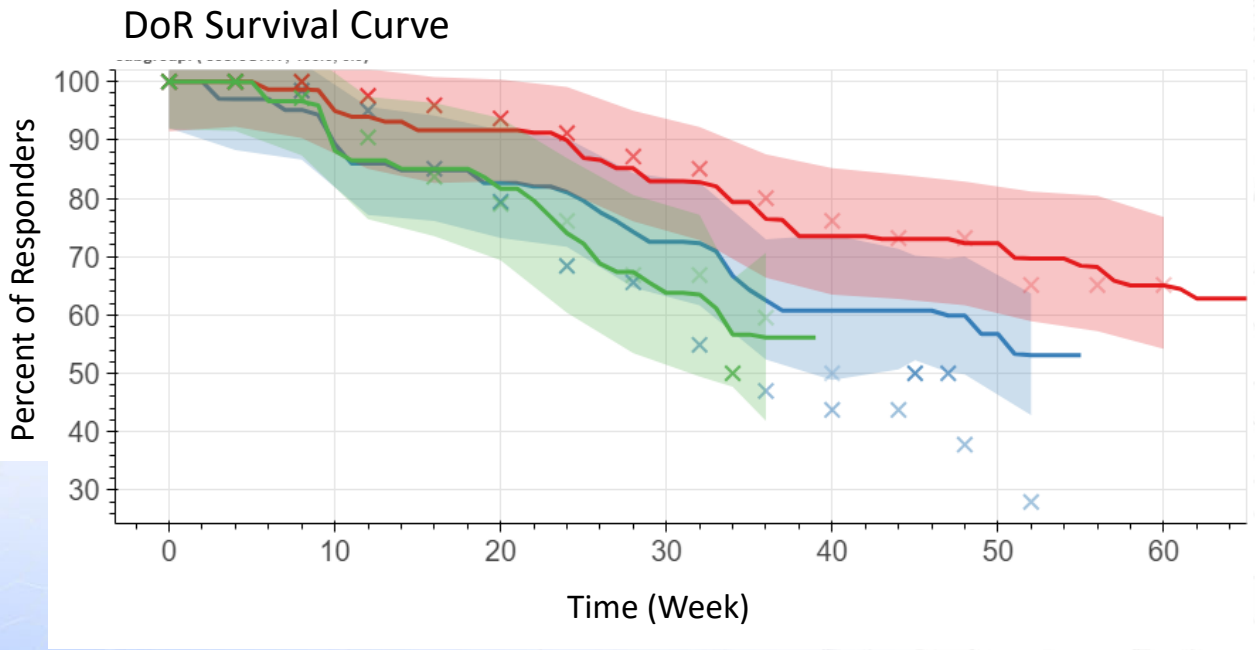

- Training data includes daratumumab and talquetamab monotherapy efficacy from the COLUMBA and MonumenTAL-1 trials. (Dara 1800mg dose not shown.)
- Model successfully validates against Tal + Dara combo therapy efficacy from TRIMM-2.
- Model's 90% confidence intervals for BOR and ORR cover the following percent of data
  - Dara (all doses): 93.3%
  - Tal (all doses): 100%
  - Tal+Dara (all doses): 75%

# Model Predicts Dara/Bort Combos




- Training data includes BOR and ORR from (bold indicates the largest trial, whose data is shown left)
  - Daratumumab: **COLUMBA**
  - Bortezomib: SUMMIT, **APEX**
- Model successfully validates against
  - Bort + Dex: CASTOR, **ENDEAVOR**, OPTIMISMM MM-007
  - Dara + Bort + Dex: **CASTOR**
- Model's 90% confidence intervals for BOR and ORR cover the following percent of data (all trials)
  - Bort: 100%
  - Dara (all doses): 93.3%
  - Bort + Dex: 63%
  - Dara + Bort + Dex: 83.3%

# Model Predicts DoR for Dara+Bort+Dex Combo




- Model training data included DoR for Bort monotherapy from SUMMIT (shown in green)
- Validation data is from
  - Bort+Dex: CASTOR, ENDEAVOR, OPTIMISMM MM-007 (blue)
  - Dara+Bort+Dex: CASTOR (red)
- Model's 90% confidence intervals cover the following percentage of DoR data points:
  - Bort mono: 100%
  - Bort+Dex: 47%
  - Dara+Bort+Dex: 100%

# Entry to Simulations Plus QSP via Consulting and/or Licensing Options

- Consulting projects
  - Fixed price with milestone-based payments
  - Time and materials with monthly payments
- Licensing
  - Available for in-house use
  - High performance grid licensing (HPGL) available
  - Some training included
- FTE
  - Simulations Plus scientist dedicated to your projects
- Consult and coach
  - Consulting project culminating in file delivery and 3 month license
  - Facilitates ongoing queries by sponsor

# Thank You

Interested in learning more? Contact:

**Steven Chang**
*President, QSP Solutions Pittsburgh*
+1-661-723-7723
steve.chang@simulations-plus.com

**Lisl Shoda**
*Assoc. Vice President & Director of Immunology*
+1-650-743-9992
lisl.shoda@simulations-plus.com

**Learn More!** www.simulations-plus.com

# Typical Savings of Biosimulation Along the Value Chain (QSP Efficacy Modeling)

| | | |
|---|---|---|
| **Prioritize targets and compounds** | Improve probability of success by optimizing the treatment approach as early as possible; avoid wasted time preclinical / clinical studies later | 6-12 months per project<br>$100K+ per study animal costs<br>$250K+ in clinical savings |
| **Better interpret preclinical and clinical data to improve strategy** | Increase confidence with early understanding of dose range required; reduce animal study sizes; reduce early clinical trial sizes; achieve more targeted and clearer efficacy outcomes in Ph II | 6-12 months per project<br>$100K+ per study animal costs<br>$250K+ in clinical savings |
| **Distinguish between responders and non-responders** | | |
| **Optimize clinical trial protocols, including optimal patient selection** | | |
| **Regulatory MOA confidence** | Answer regulatory questions at time of submission (e.g., mechanistic insight into therapeutic effects) | 6 months per project |
| **Prediction of combination therapies to expand market options** | Understand options for market expansion and better disease coverage; patent extension | $1M+ in new products / patent life |

**Typical total savings per project:**

12-18 months acceleration to market = sales

$100K-$1M+ savings

# Typical Savings of Biosimulation Along the Value Chain (QST Safety Modeling)

| | | |
|---|---|---|
| **Pick your safest lead candidate** | Improve your probability of success by optimizing safety as early as possible; avoid wasted time and wasted preclinical and clinical studies later | 6-12 months per project<br>$100K+ per study animal costs<br>$250K+ in clinical savings |
| **Improve safe dose projection via mechanistic understanding**<br>**Compare to your competition's safety margin in advance**<br>**Overcome suspicions raised by external stakeholders or animal studies** | Increase confidence with early understanding of upper dosing bounds for safety; reduce animal study sizes; avoid later stage dose creep without safety context; reduce early clinical trial sizes | 6-12 months per project<br>$100K+ per study animal costs<br>$250K+ in clinical savings |
| **Regulatory flexibility** | Answer regulatory questions at time of submission (e.g., mechanistic insight into known safety signals) | 6 months per project |
| **Avoid late-stage clinical safety-related failures** | Reduction of unnecessary human testing | $1M+ per clinical study + months |

**Typical total savings per project:**

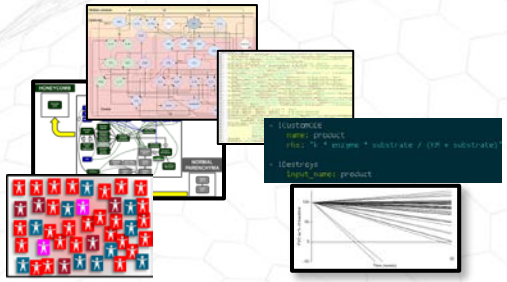
12-18 months acceleration to market = sales

$100K-$1M+ savings

# Simulations Plus Has Expertise and Experience to Develop QSP Models to Predict Efficacy Across Therapeutic Areas

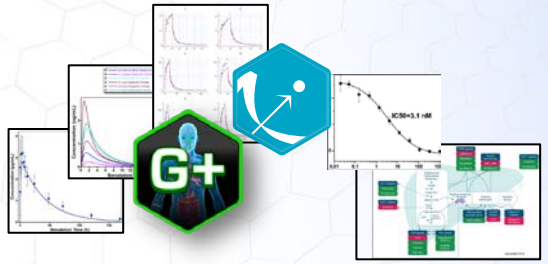
## Identify therapeutic area and disease

- Collaborative with project sponsors
- Oncology, fibrosis, neurology, autoimmune, etc.



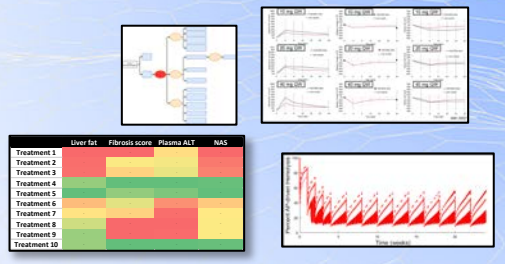
## Develop QSP Model

- Summarize key biochemical and clinical data
- Capture key pathophysiological processes and ontology with equations
- Relevant clinical outputs
- Develop SimPops
- Simulate SOC treatments




## Represent novel treatments

- Pharmacokinetics (GastroPlus, Monolix)
- Pharmacodynamics
- Mechanism of action




## Predict efficacy of novel treatment

- Optimize clinical trial protocols
- Optimize dosing regimens
- Combination with SOC treatments
- Efficacy comparison vs. SOC treatments
- Confirm in vivo drug MoA
- Identify characteristics of responders vs. non-responders