EFPIA/EMA M&S workshop

Quantitative Systems Pharmacology in Drug Development

- A Pharma Perspective -

Integrating Knowledge

Enhancing Decisions

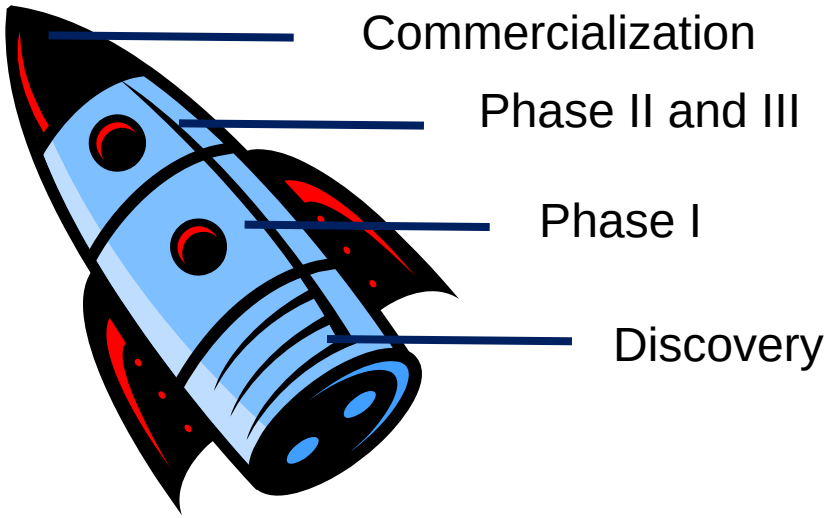
Sandy Allerheiligen, PhD, Vice President

Thomas Kerbusch, PhD, Sr Director

Modeling & Simulation, Merck

Understanding the Critical Questions

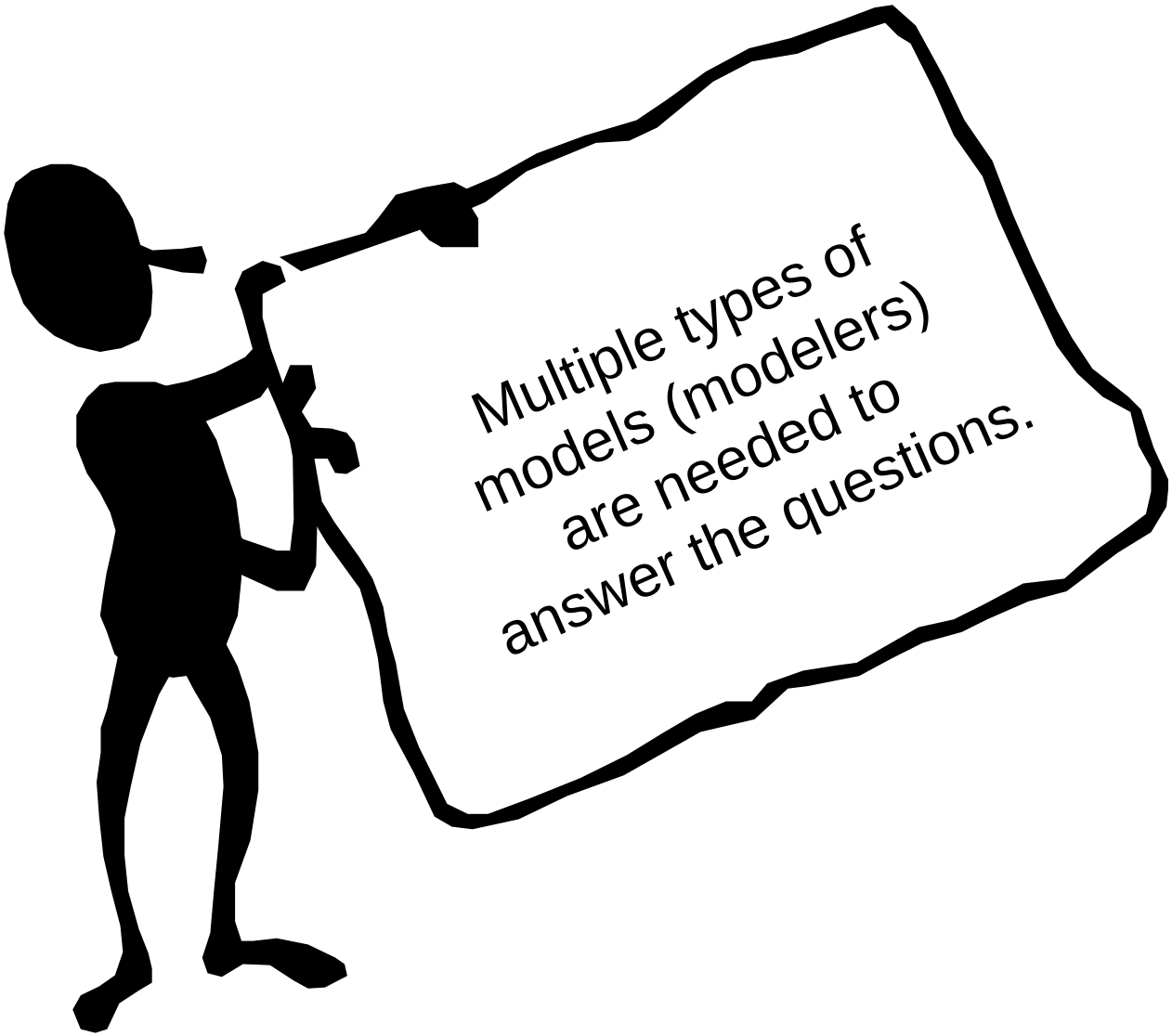
- How much improvement is required in efficacy or safety to truly be Best in Class or First in Class? How will we know and when?
- What dose is required? Are there subsets of patients who respond differently? Why?



- Do we understand variability and uncertainty in critical biomarker? How does it relate to clinical outcomes?
- Based on nonclinical results, can human efficacious dose be predicted?

Critical questions need quantitative answers to enable decision making

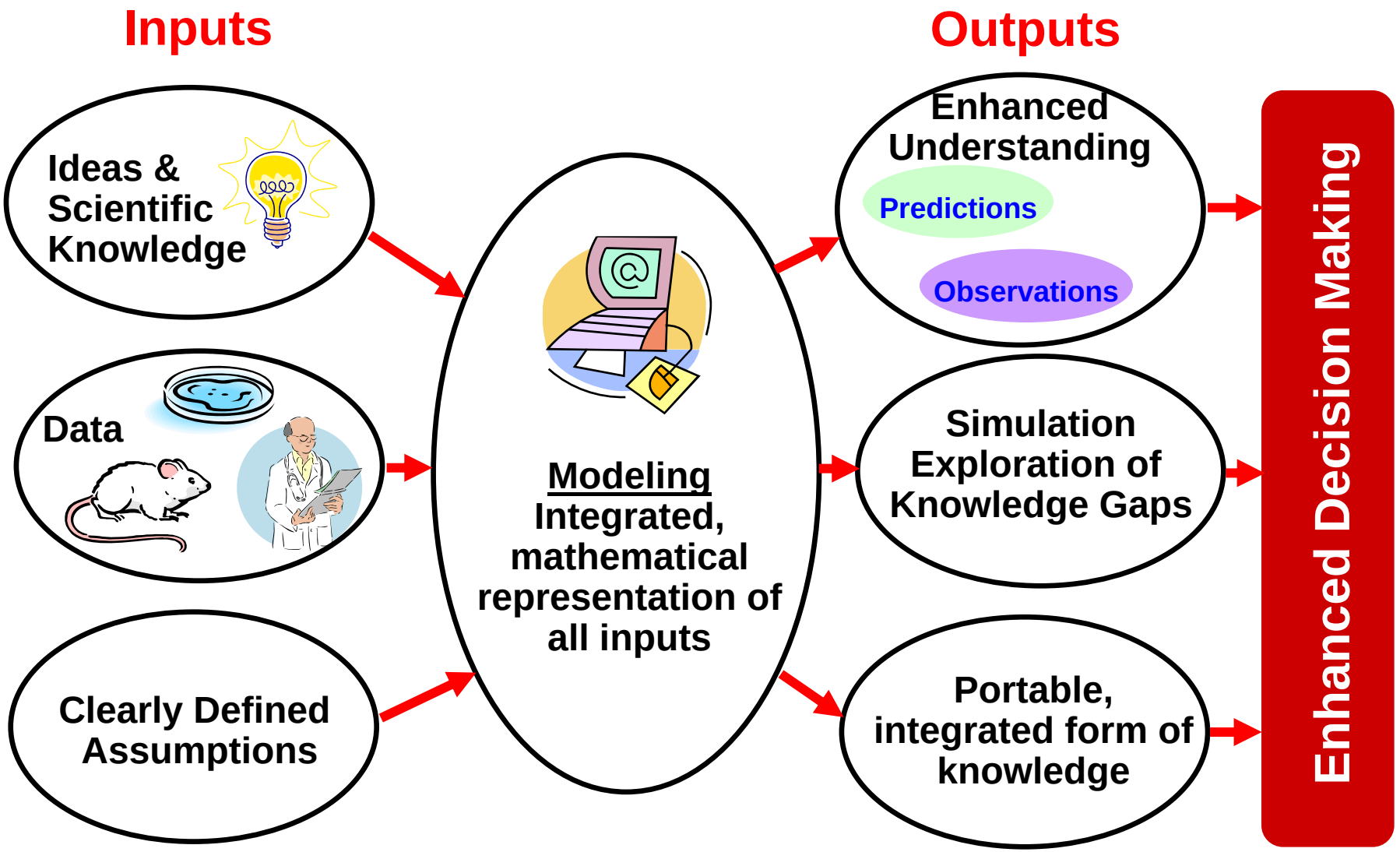
Modeling and Simulation



Quantitative Systems Pharmacology

- Defined as an approach to translational medicine that combines computational and experimental methods to elucidate, validate and apply new pharmacological concepts to the development and use of small molecule and biologic drugs.
- QSP will provide an integrated “systems-level” approach to determining mechanisms of action of new and existing drugs in preclinical and animal models and in patients.
- QSP will create the knowledge needed to change complex cellular networks in a specified way with mono or combination therapy, alter the pathophysiology of disease so as to maximize therapeutic benefit and minimize toxicity and implement a “precision medicine” approach to improving the health of individual patients.
- Quantitative and Systems Pharmacology in the Post-genomic Era: New Approaches to Discovering Drugs and Understanding Therapeutic Mechanisms. *An NIH White Paper by the QSP Workshop Group – October, 2011.* http://www.nigms.nih.gov/News/Reports/201110-syspharma.htm

How are Quantitative Systems Pharmacology Models Developed?



Quantitative Systems Pharmacology: Model-Based Drug Development Continuum

Discovery | Early Development | Late Development

Biological Modeling

- Genetic Pathway
- Systems Biology
- Pathway / Pathogen Dynamics
- Physiology models
- Disease Models
- Molecular Modeling
- Simulation
- ...

Pharmacological Modeling

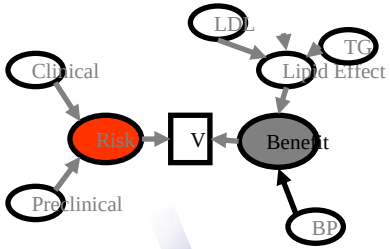
- PK Models
- PK/PD Models
- Biomarker Models
- Population Models
- Disease Models
- Natural History of Disease
- Disease Progression Models
- Trial Simulation
- ...

Statistical Modeling

- Population Models
- Trial Simulation
- Epidemiologic Models
- Disease Models
- Outcomes Models
- Drop Out Models
- Adherence Models
- Enrollment Models
- Utility Decision Models
- ...

Creating multidisciplinary models integrating biological, pharmacological, & clinical knowledge

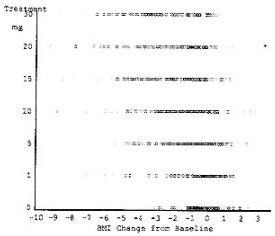
Quantitative Decision Models



Literature database

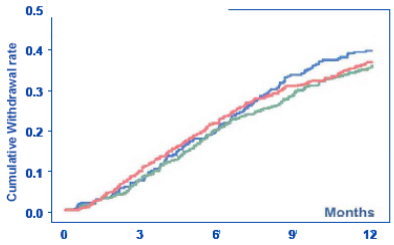
Ref Code	Author	Journal	Year	Number of centers	Primary Anti-obesity Drug Studied	Study Population Nationality	Number arms	Duration	Diet Category	Exercise Category	Behav Mod Category	Num Enrolled
16	Wirth, Alfred	JAMA	2001	111	Sibutramine	German	3	48 weeks	Moderate	yes	yes	1001
19	McNulty	Diab Care	2003	21	Sibutramine	Mixed Norther European	3	12 month	Mild	no	no	195
20	Wadden	Arch Intern Med	2001	1	Sibutramine	USA	3	12 mos	Mod/Severe	yes	Yes	55
22	Fanghanel	Inter J Ob	2000	1	Sibutramine	Mexican	2	6 mos	Mild	no	no	109
24	Bray	Ob Res	1999	7	Sibutramine	USA	7	24 weeks	Moderate	yes	no	1047
25	Smith	J Fam Prac	2001	1	Sibutramine	UK ?	3	12 month	Mild	no	Yes	485
28	Bray	Ob Res	1996	1	Sibutramine	USA	7	24 weeks	Moderate	yes	no	173
31	Hauner	Exp Clin Endo Diab	2004	33	Sibutramine	German	2	12 Month	Moderate	Yes	Yes	362
32	Fanghanel	Advan in Therp	2003	23	Sibutramine	Mexican	2	6 month	Mild	no	no	57
33	Sanchez-Reyes	Clin Ther	2004	1	Sibutramine	Mexican	2	12 month	Mild	no	no	86
34	Swinburn	Inter J Ob	1996	1	Dexfenfluramine	New Zealand	2	36 Weeks	Mild	no	yes	97
36	James	Lancet	2000	8	Sibutramine	Northern European	2	24 month	Moderate	Yes	Yes	605
					Rimonabant	North America	2	2 years				
					Rimonabant	Europe	2	1 year				
					Rimonabant	Lipids	2	1 year				

Variability model

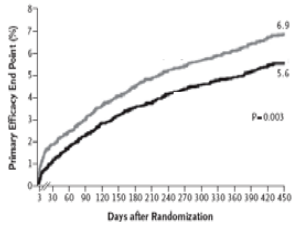


Integrated Models

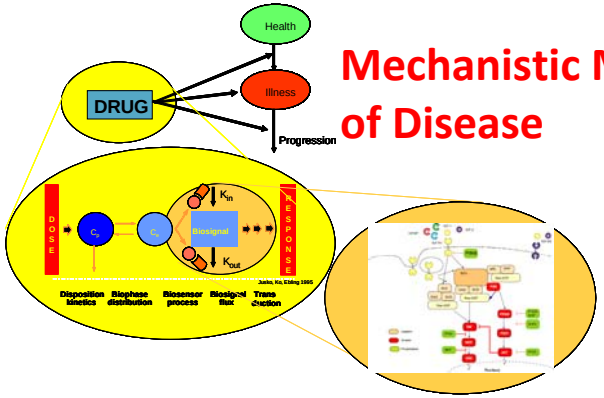
Dropout model



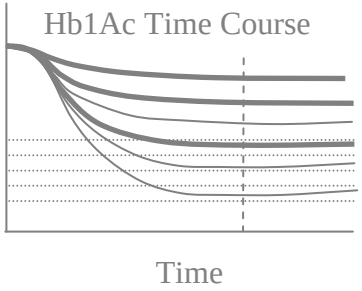
Genomics & Outcome Models



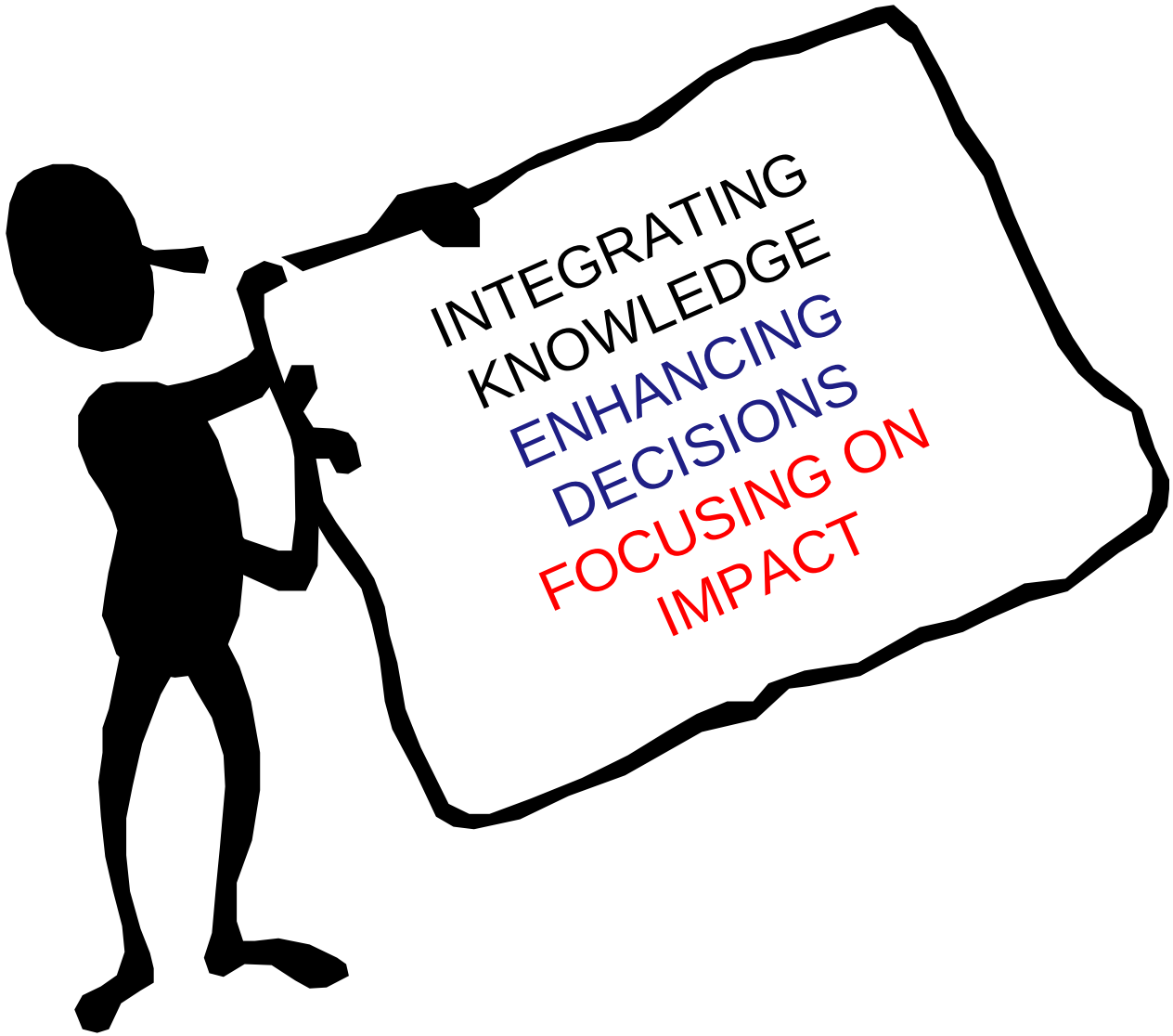
Mechanistic Models of Disease



PK-PD models and longitudinal models with potential covariates such as age, sex, severity of disease, etc.



Modeling and Simulation



Using M&S to Aid Early Development of HIV Compounds

Key questions:

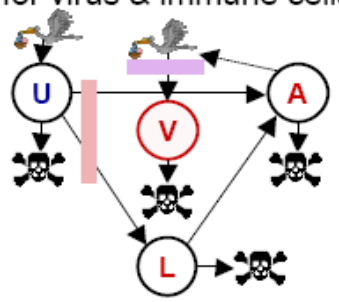
- Which compounds are most likely to succeed given current competition?
- What doses / study design should we use for POC study?

PK → **Estimate of in vivo IC50 and effective dose** → **Viral Dynamics** → **Predicted Outcome of Clinical Studies**

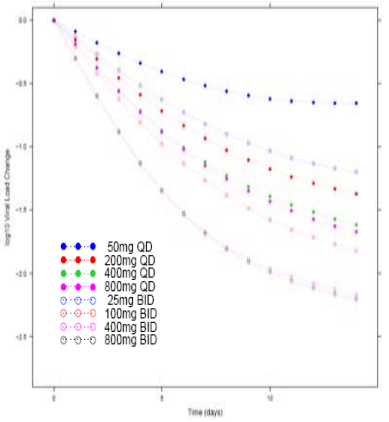
Determined by scaling from in vitro/ preclinical data or from early clinical data, where available

- Determined in vitro IC95 for compound and key SOC in same viral spread assay
- Determined in vivo IC50 and PK from published data
- Determined dose of NME that would match PK/IC95 ratio for SOC
- Applied to multiple mechanisms of action

Typical model:
Viral inhibition = conc. / (conc. + IC50); (1-inhibition) multiplies infectivity rate in predator-prey equations for virus & immune cells.



U=uninfected T-cells
A=actively infected CD4 cells
L=latently infected CD4 cells
V=virus



L. Wenning, M. Rizk, W. Poland (Pharsight), 2010

Is there a therapeutic window that allows new molecule (NME) to be "best in class"?

Questions

- *Is there a target exposure with associated stroke and major bleeding profile that is meets target product profile?*
- *For target exposure, what is the expected mean effect on QTc?*
- *Can exposure variability sufficiently be controlled?*

Data

- *Exposure and Thrombin Generation (TG) data*
  New Molecule
  Comparator molecules
- *Stroke and bleeding data*
  Comparator
- *Exposure and QTc data*
  NME

Linked models

Exposure - TG

TG – Stroke Prevention

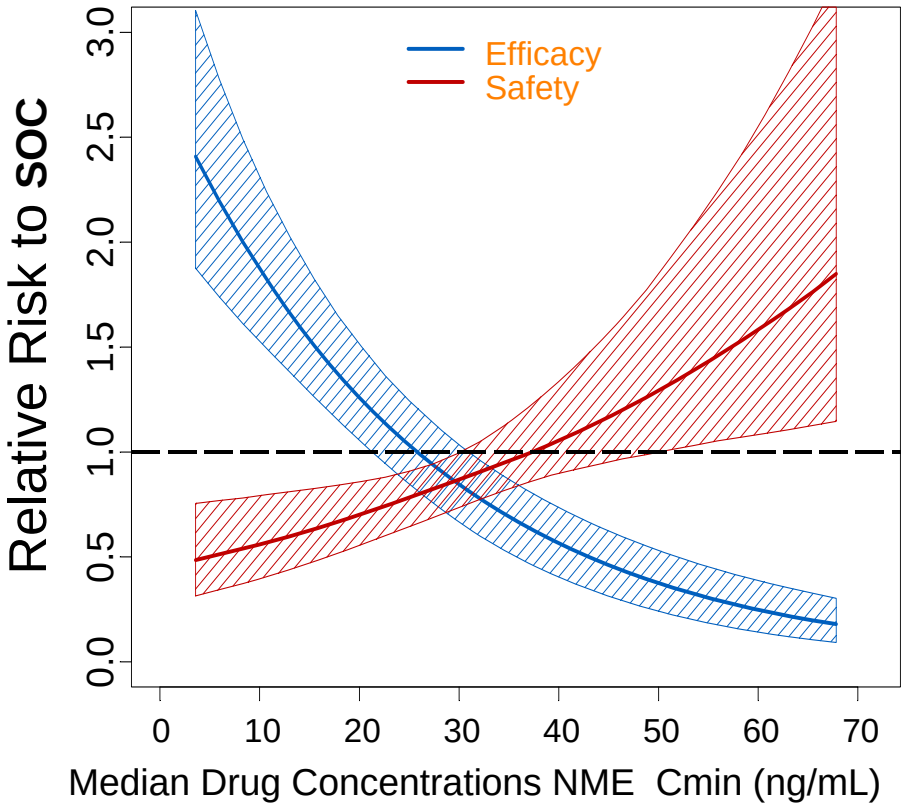
TG – Bleeding Risk

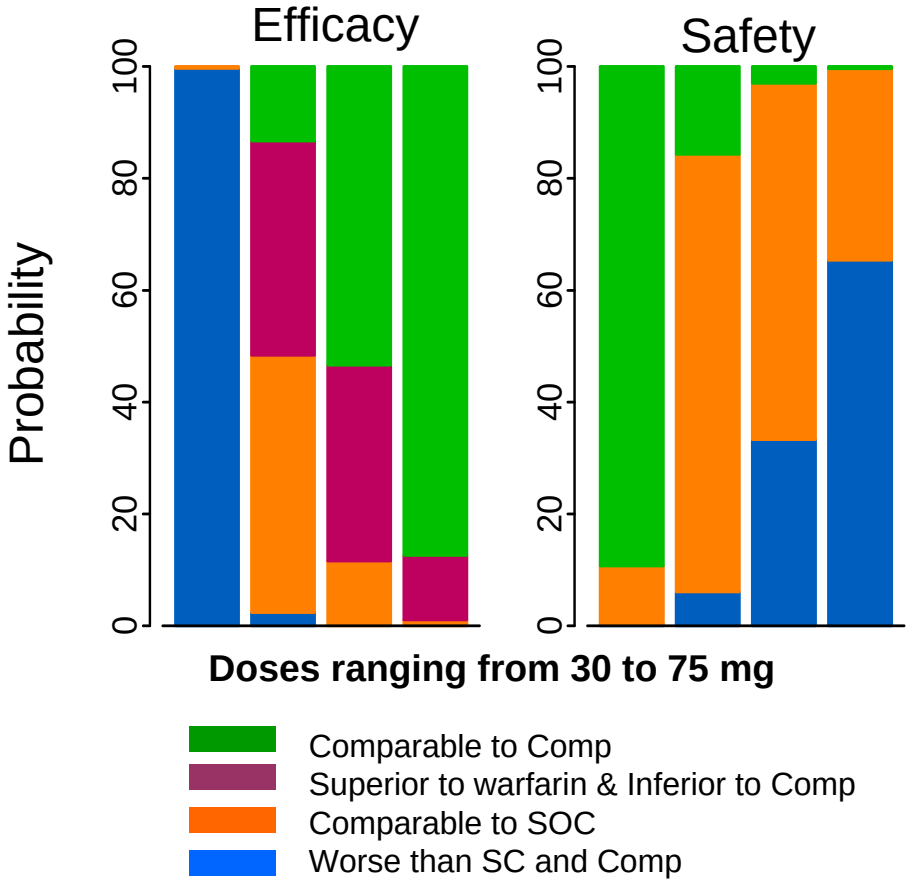
Exposure - QTc

Leveraging an internal biomarker study and phase I and II trials plus external data for hundreds of patients on comparator molecules, integrated models were developed to link relationship between the biomarker and variability in exposure to understand probability of preventing stroke while minimizing bleeding risk and potential for impact on QTc was also evaluated.

Team Recommendation: Discontinue
No dose allows NME to be BIC

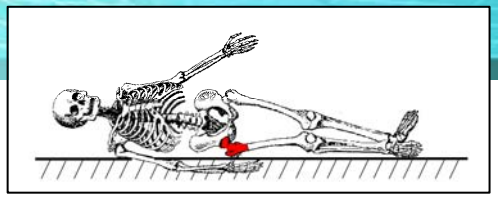
Based on 5000 simulations at each concentration

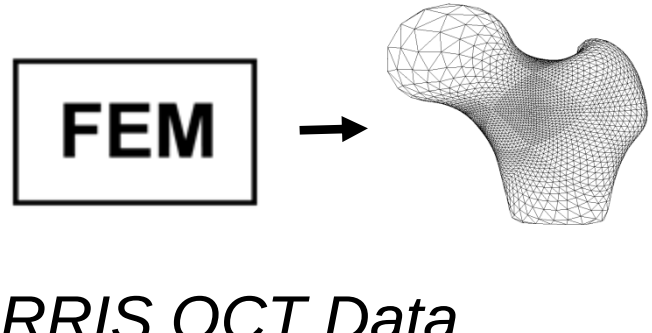


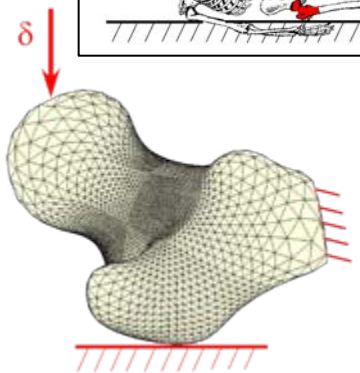


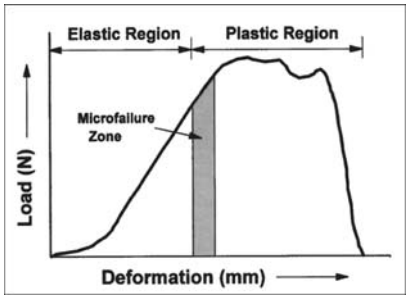
Prior to M&S effort, team was struggling to made a decision and design Phase III trial based on existing internal data. By leveraging critical biomarker and published outcomes, simulations for 1000s of patients from integrated models allowed team to explore a range of questions and assumptions. Team was able to make recommendation and present the modeling results.

FE-Simulation of *Fall Loading*

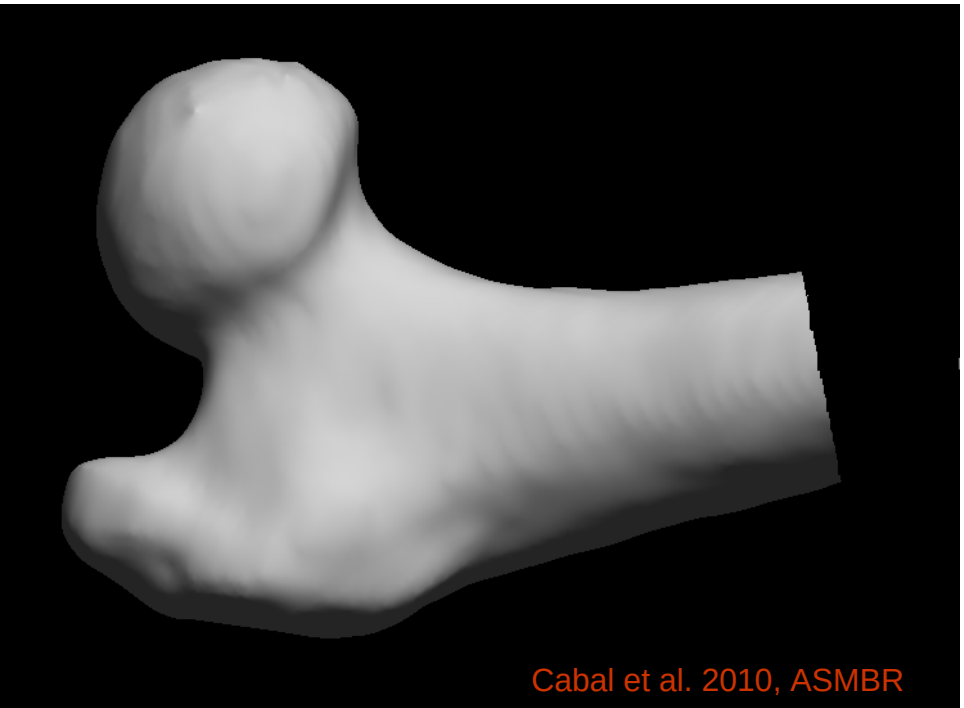


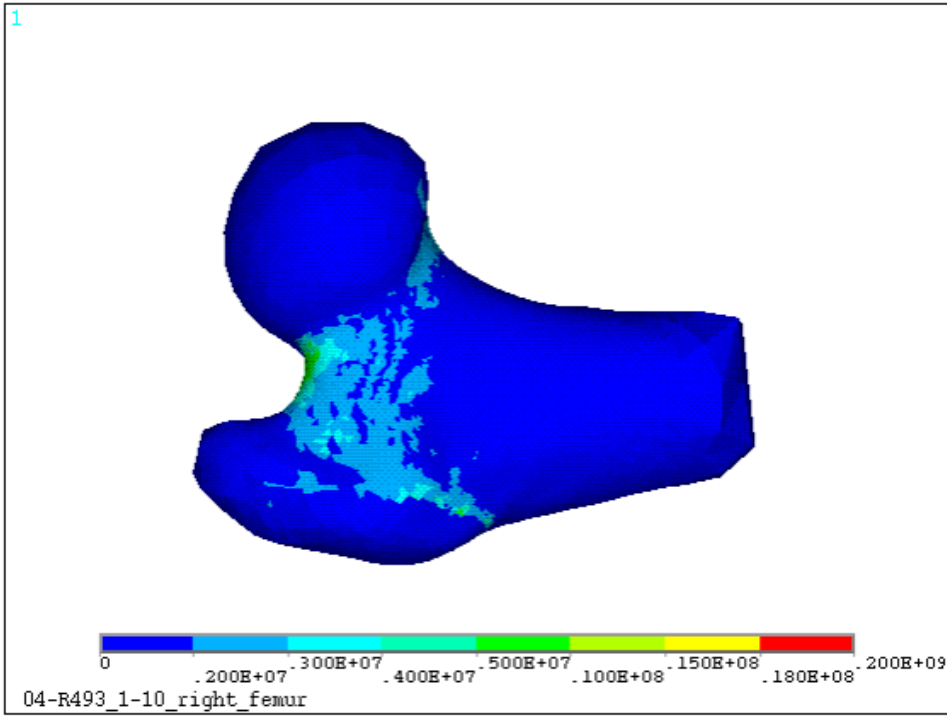




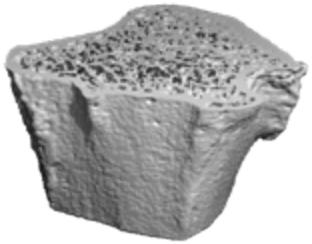


ORRIS QCT Data

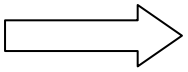


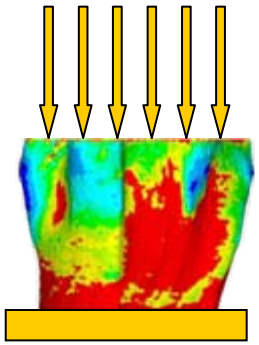


Finite Element Analysis of Radius Images Demonstrates Increased Bone Strength with Odanacatib in Rhesus



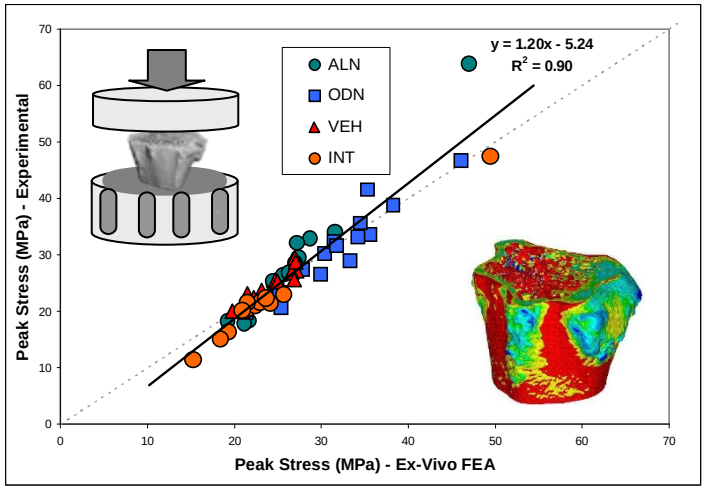
High resolution image



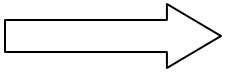


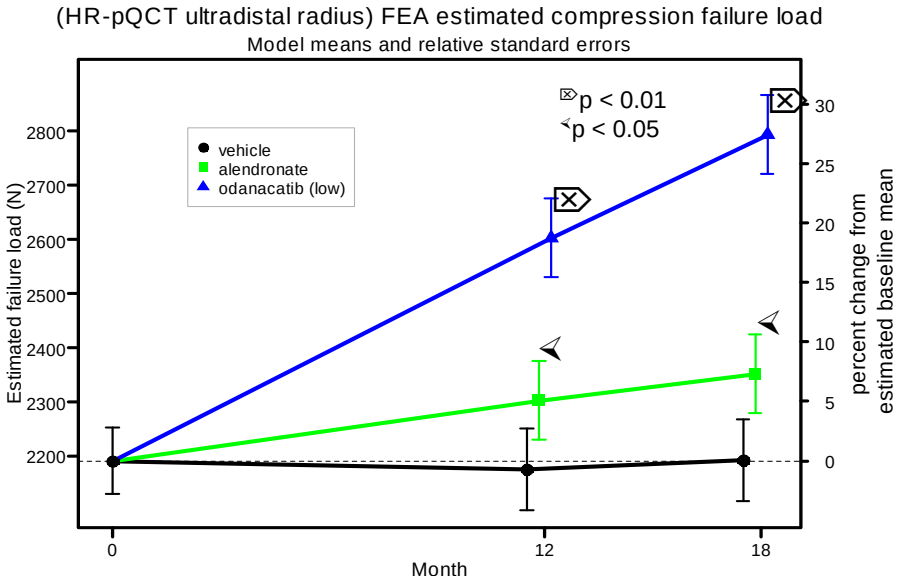
Computational estimate of bone strength

Validation of FEA strength estimates with ex vivo mechanical testing



Using Validated FEA procedure





FE-Estimated Peak Load increased 27% for ODN, 7% for ALN, and unchanged for VEH after 18 months of treatment

Cabal et al. 2011, 3rd Joint ECTS-IBMR Meeting

Key Messages

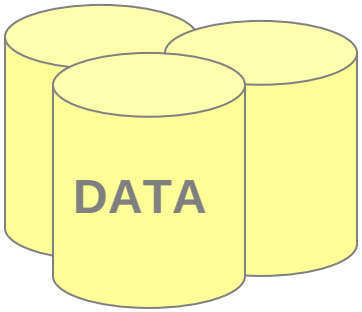
- Question-driven Modeling and Simulation: Enables team's ability to understand and explore impact of variability and uncertainty
- Models are data driven (clinical and nonclinical derived from internal and external experiments/ trials). Assumptions are transparent.
- Quantitative Systems Pharmacology is new mantra: Integrated, multidisciplinary models developed through quantitative disciplines and the team.
- Ultimately can explore results of trials/ outcomes trials could be conducted thousands of times
- Models should be continuously developed over time
- Tools and modeling capability must be flexible and continuously refined.

Imagine if…

- Modeling & Simulation capability is increasingly **flexible and adaptable** to the evolving quantitative needs in MRL
- Virtual workbench brings **integrated databases and previously developed models at our finger tips**
- **Real-time visualization and simulation** allow us to see impact of assumptions, comparison of models, understand uncertainty, …
- **Comparator models** support each of our Best in Class programs in discovery and development
- **Model supported trial design, clinical planning and trial avoidance** in all our early and late stage development programs
- **Model aided drug approvals** are achieved
- **Quantitative decision making** which integrates knowledge across discovery / development continuum
- **Integrated model supported drug discovery and development** paradigm becomes institutionalized
- **Models can be ultimately be used at the "bedside"** to optimally inform dose selection, patient selection and that the models update in real-time with each patient

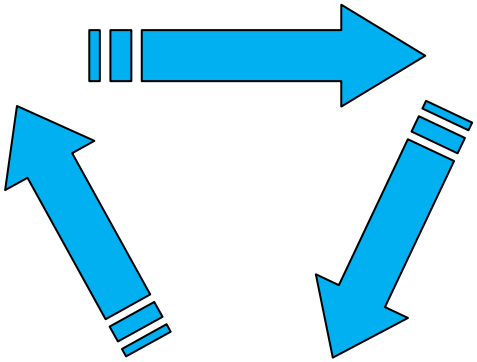
Modified from a slide provided by Rick Lalonde, PhD

Learning Cycles

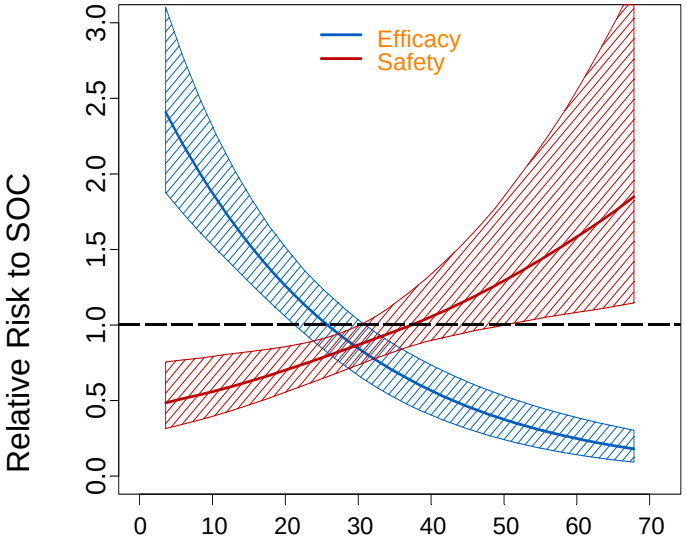


EXPERIMENTS / CLINICAL TRIALS (Internal and External)

INFORMATION

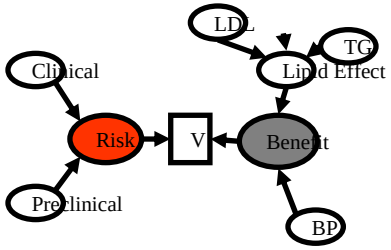


INFORMED DECISIONS



INCREASED EFFICIENCY AND DATA QUALITY:

Data Curation, Historical Data, and Improved Experimental / Trial Designs



GAINING INSIGHTS:

Modeling, Simulation, Learning

QUANTITATIVE DECISIONS:

Integrating Knowledge, Enhancing Decisions