CERTAINTY DISCOVERY

CERTARA | Chemaxon

Early feasibility assessment: using biosimulation to guide design and prioritization in early discovery

Piet van der Graaf

Certara

Senior Vice President, Quantitative Systems Pharmacology

Early Feasibility Assessment:

Using Biosimulation to guide Design and Prioritization in Early Discovery

Piet van der Graaf. PharmD, PhD

Senior Vice President and Head of Quantitative Systems Pharmacology

Professor of Systems Pharmacology, Leiden University
Professor of Pediatrics, Cincinnati Children's Hospital Medical Center
Editor-in-Chief *Clinical Pharmacology & Therapeutics*

Certainty Discovery, Frankfurt
5 November 2025

CERTARA

Model-Informed Drug Development (MIDD)

2007

Model-based Drug Development

RL Lalonde[1], KG Kowalski[2], MM Hutmacher[1], W Ewy[2], DJ Nichols[1], PA Milligan[1], BW Corrigan[1], PA Lockwood[1], SA Marshall[1], LJ Benincosa[1], TG Tensfeldt[1], K Parivar[1], M Amantea[1], P Glue[1], H Koide[1] and R Miller[1]

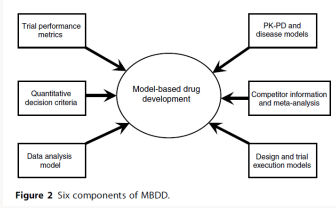


Figure 2 Six components of MBDD.

2013

Model-Based Drug Dev... ational Approach to Effici... Drug Developmen...

Quantitative Systems Pharmacology

PA Milligan[1], MJ Brow... an[1], PH van der Graaf[3,1], N Benson[4,11], G Nucci[5], DJ Nichols[5], k... na[7], S Krishnaswami[6], S Zwillich[8], D Gruben[2], RJ Anziano[2], TC Stock[9] a...

$70M total savings in first year

2025

Impact of Model-Informed Drug Development on Drug Development Cycle Times and Clinical Trial Cost

Vaishali Sahasrabudhe[1]*, Timothy Nicholas[1], Gianluca Nucci[2], Cynthia J Musante[2] and Brian Corrigan[3]

$5M & 10 months savings per program

ICH harmonisation for better health

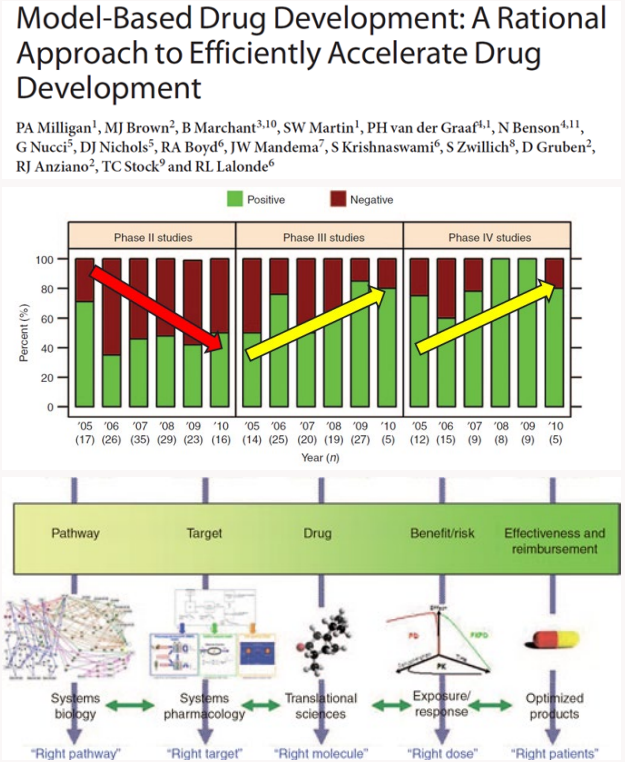
INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

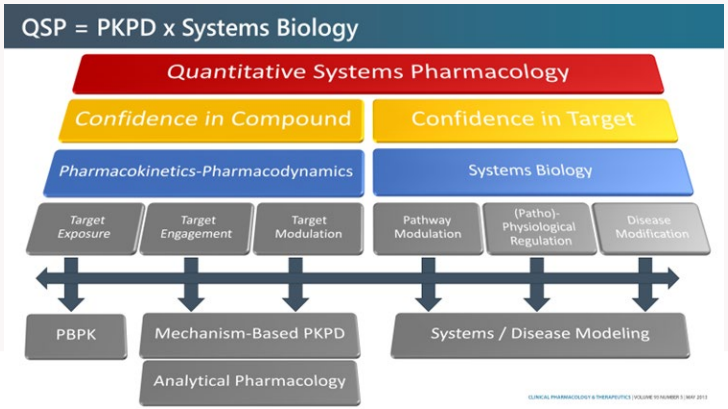
GENERAL PRINCIPLES FOR MODEL-INFORMED DRUG DEVELOPMENT

M15

Quantitative Systems Pharmacology (QSP)



- A mechanistic bio-simulation approach that combines computational modeling and data to examine the quantitative relationship between a drug, the biological system, the disease process and a biomarker or clinical readout
- Re-usable platform models that integrate literature, data and knowledge of biology, pharmacology and disease
- Human models: allow for simulation of virtual trials and generation of virtual patients



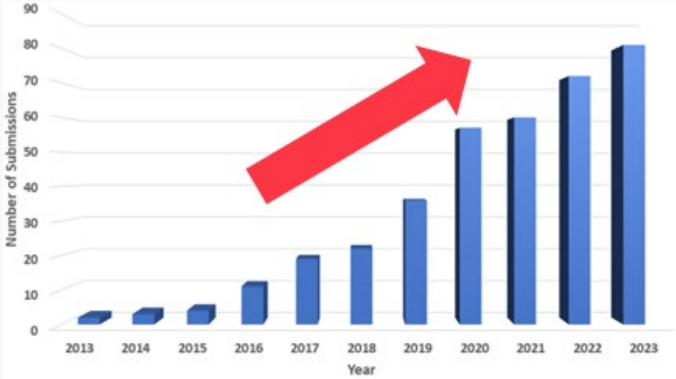
Regulatory Adoption of QSP

DOI: 10.1002/psp4.13208

ARTICLE

Landscape of regulatory quantitative systems pharmacology submissions to the U.S. Food and Drug Administration: An update report

Jane P. F. Bai | Guansheng Liu | Miao Zhao | Jie Wang | Ye Xiong | Tien Truong | Justin C. Earp | Yuching Yang | Jiang Liu | Hao Zhu | Gilbert J. Burckart



https://www.ema.europa.eu/en/events/hma-ema-multi-stakeholder-workshop-reporting-qualification-mechanistic-models-regulatory-assessment

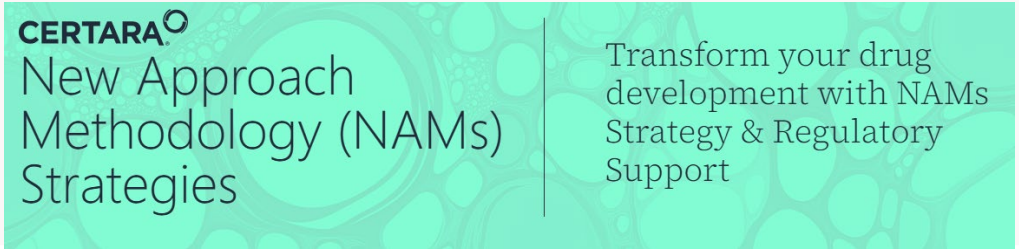
QSP Aligned with Regulatory NAM Initiatives

FDA NEWS RELEASE

FDA Announces Plan to Phase Out Animal Testing Requirement for Monoclonal Antibodies and Other Drugs

For Immediate Release: April 10, 2025

- Advanced Computer Simulations: The roadmap encourages developers to leverage computer modeling and artificial intelligence to predict a drug's behavior. For example, software models could simulate how a monoclonal antibody distributes through the human body and reliably predict side effects based on this distribution as well as the drug's molecular composition. We believe this will drastically reduce the need for animal trials.

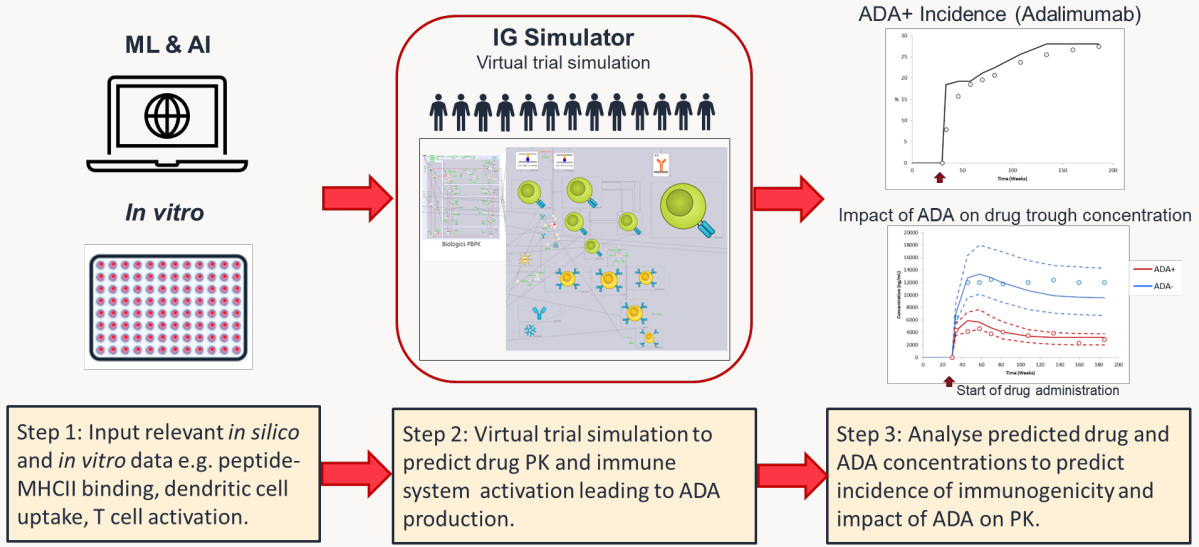


https://www.certara.com/solutions/non-animal-navigator/nam-strategies/

In Silico NAM: Predicting Clinical Immunogenicity

Front. Immunol. 16:1677925.
doi: 10.3389/fimmu.2025.1677925

Towards new approach methodologies for biological therapeutics: a novel model-informed metric to assess immunogenicity risk

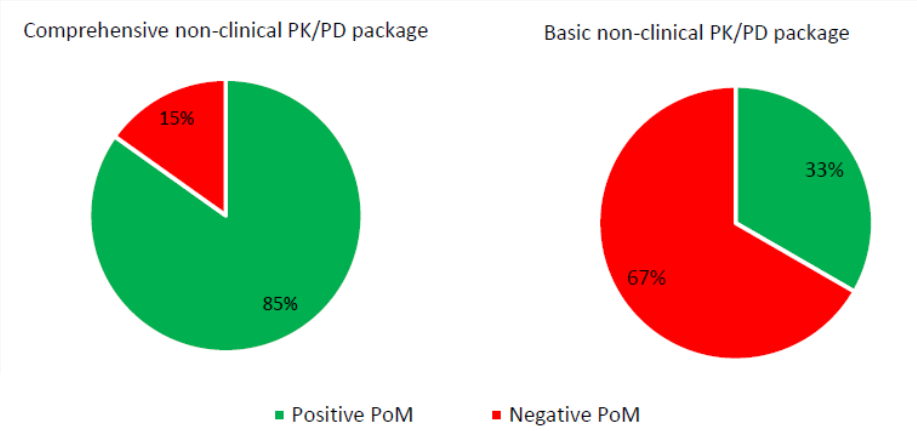


IG Simulator correctly predicts impact of ADAs on PK in ~80% of cases

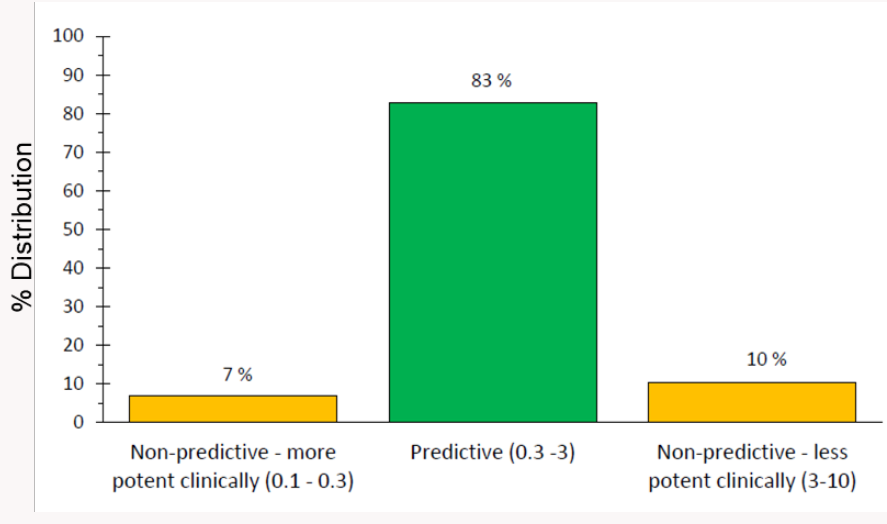
Preclinical Bio-Simulation Increases Probability of Clinical Success ~3-fold

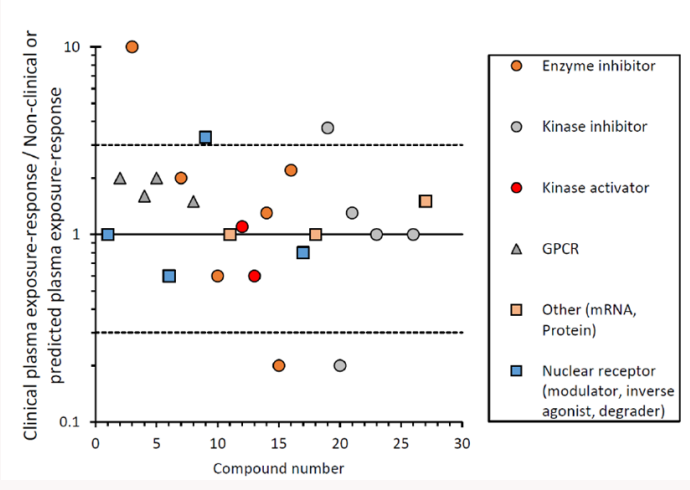
Drug Discovery Today • Volume 30, Number 7 • July 2025

Translational PK/PD: a retrospective analysis of performance and impact from a drug portfolio



Preclinical Bio-Simulation Predicts Clinical Exposure

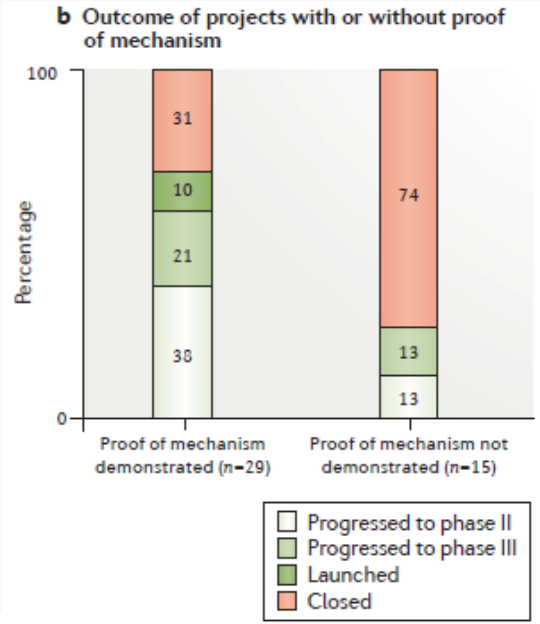




Preclinical Bio-Simulation Improves Overall Success

Probability
Proof of Mechanism
↑3-fold

Impact of a five-dimensional framework on R&D productivity at AstraZeneca



Attrition
74% → 31%

doi:10.1038/nrd.2017.244

MABS
2023, VOL. 15, NO. 1, 2192251
https://doi.org/10.1080/19420862.2023.2192251
Taylor & Francis
REVIEW
OPEN ACCESS

Mechanistic PK/PD modeling to address early-stage biotherapeutic dosing feasibility questions

Joshuaine Grant†, Fei Hua†, Joshua F. Apgar, John M. Burke, and Diana H. Marcantonio

Early Feasibility Assessment (EFA)

Platform-based bio-simulation workflow to address key questions in early discovery

What is the optimal target in a biological pathway?

Is it better to target the ligand or the receptor?

Is it feasible to achieve the intended pharmacology in the clinic?

What are the required drug properties to achieve the desired pharmacology at feasible doses?

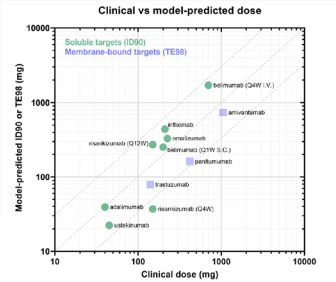
EFA requires no *in vivo* animal data, no *in vitro data*, no compounds

FIT FOR PURPOSE

Aligned with drug discovery requirements and cycle times:

- Consistent, reliable
- Turnaround days-weeks

VALIDATED



IMPACT

- Shorten discovery timelines
- Better clinical candidates
- Kill early: redirect resources to back the winners

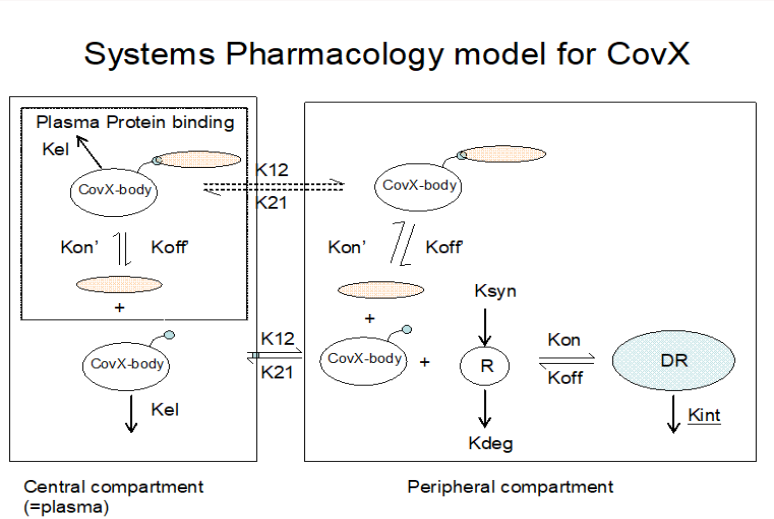
RETURN ON INVESTMENT

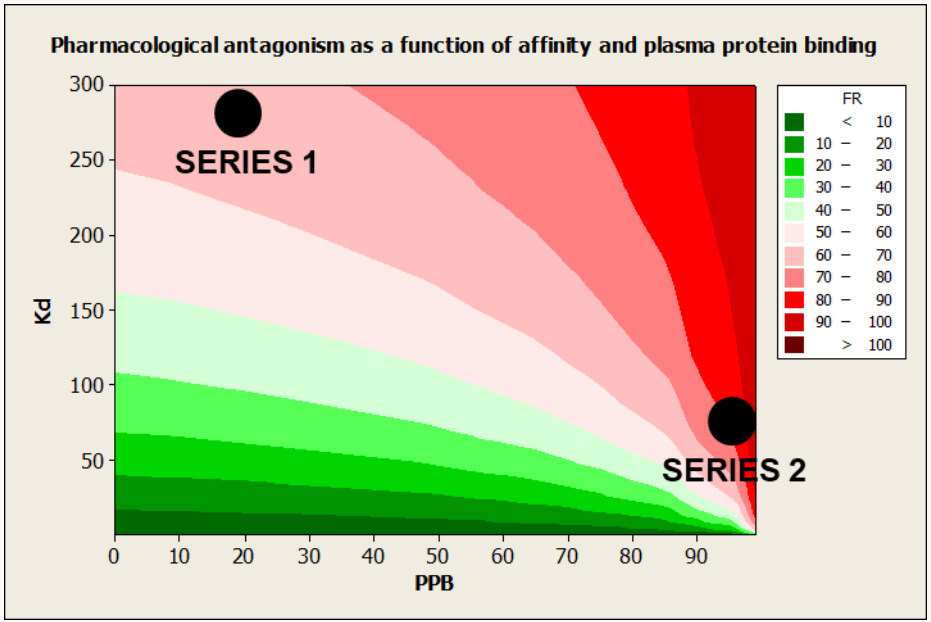
EFA at scale can save $10-$100M at portfolio level

doi: 10.3389/fphar.2022.864768

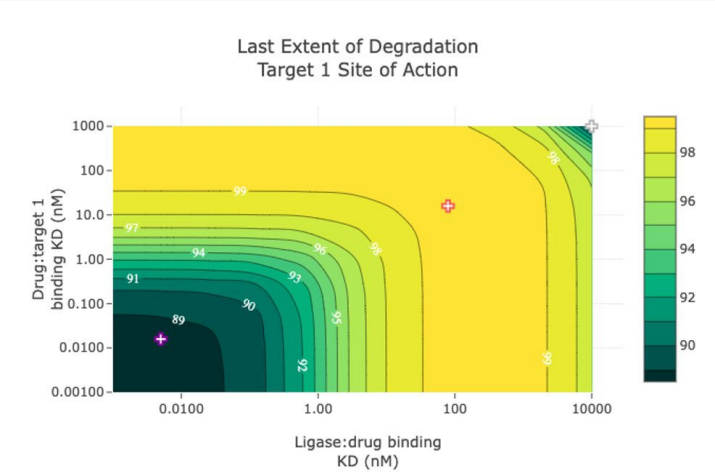
EFA Case Study 1: Fusion Protein for Immunology/Pain

- EFA applied to guide chemistry strategy
- Resulted in change of priority from series 2 to series 1



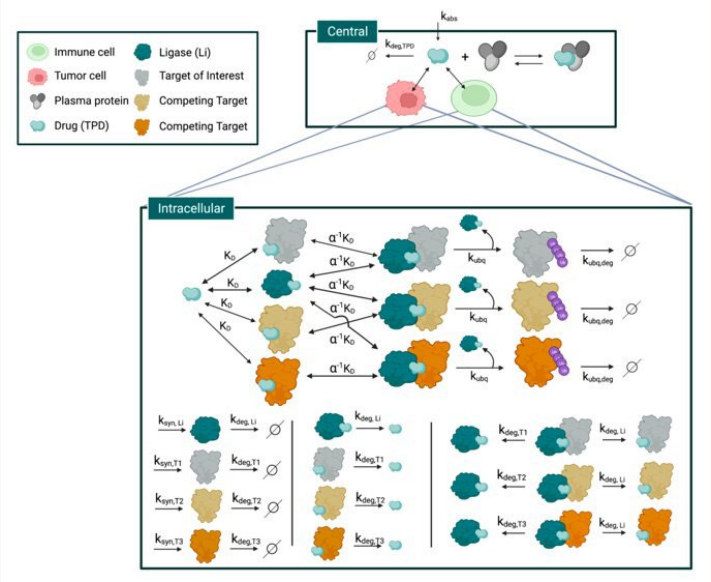


EFA Case Study 2: PROTACs



EFA identifies the optimum value for E3 Ligase and Substrate for a PROTAC

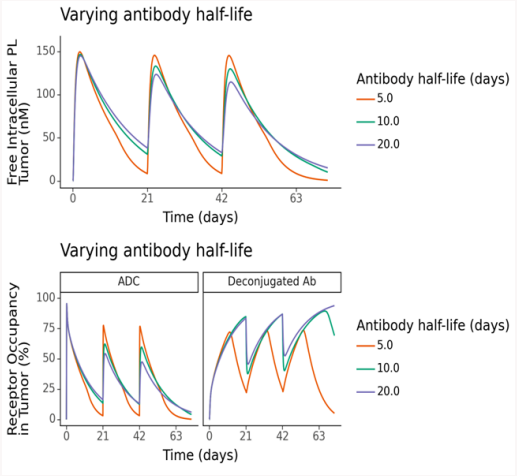
Complex modalities can have trade offs between parameters



With combinatorial drug design spaces, it is impractical to explore the space experimentally. Modeling increased the chance of success by focusing on the feasible design space.

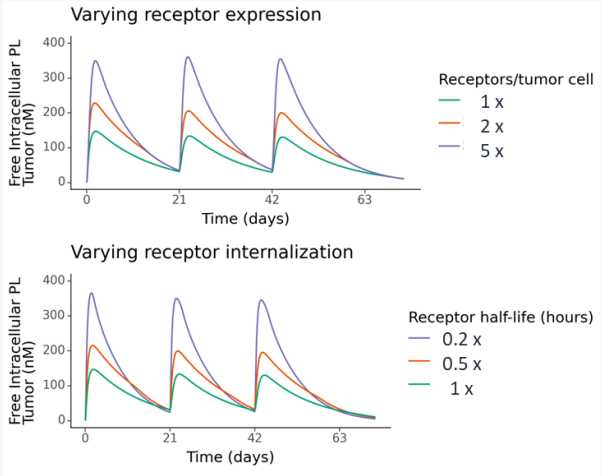
EFA Case Study 3: ADCs

Antibody half life



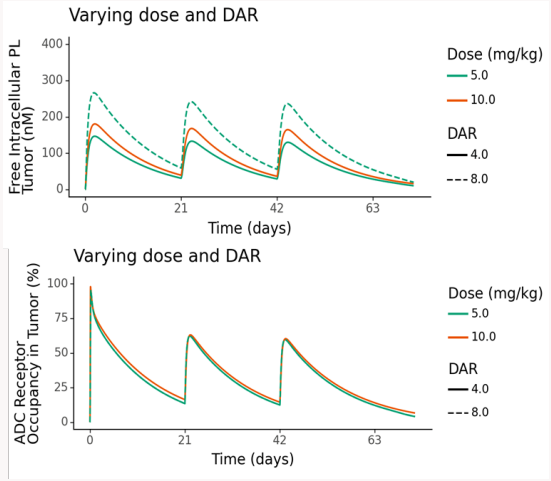
- Increasing drug half-life could lead to decreasing efficacy due to competition from the naked-antibody

Target expression/turnover



- Increasing target expression level and internalization rate can both lead to increased efficacy

Drug-Antibody Ratio

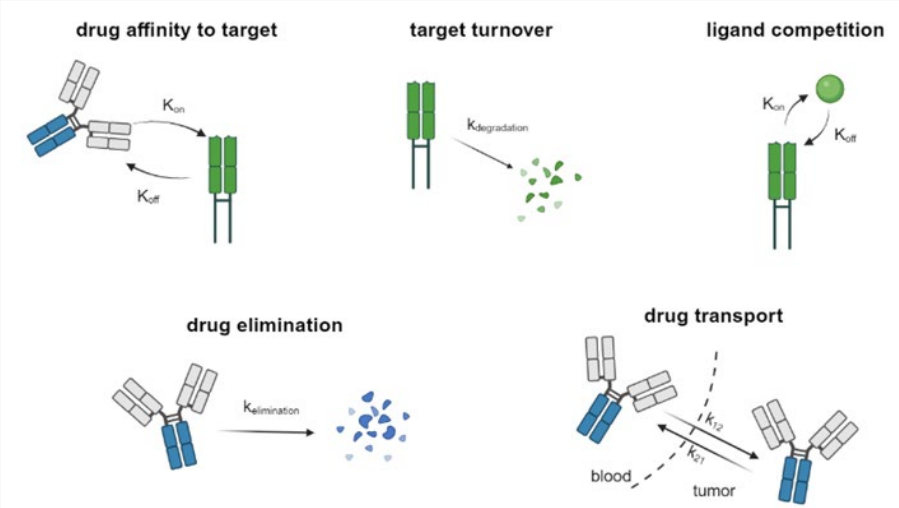


- Once antibody binding is saturated, increasing the dose will not increase the efficacy further, while toxicity may continue to increase
- Increasing DAR allows a bigger increase in efficacy compared to dose increase

EFA Case Study 4: Bispecific mAbs

Goal: use EFA **at scale** to efficiently identify the bispecific drug properties that will match metrics of monospecific clinical competitors before building the molecules

- ~30 Bispecifics tested in 5 Indications
- ~5 Million simulations
- Delivered in ~6 months



EFA Case Study 4: Bispecific mAbs

					Monthly dosing			1.5 month dosing			2 month dosing			Clinical evidence Tier	
Molecule	Target Pair	Valency	Indication	SoA	Kd1	Kd2	t1/2	Kd1	Kd2	t1/2	Kd1	Kd2	t1/2	Target 1	Target 2
1	A x B														
2															
3															
4															
5															
6															
7															
8															
9															

Most favorable	Intermediate	Less favorable	Infeasible/ least favorable
KD ≥ 100 nM	**KD** 10 - 99 nM	**KD** < 10 nM	**KD** None
T1/2 10 days	**T1/2** 20 days	**T1/2** 30 days	**T1/2** None
Clinical evidence Approved/effic. dose in desired indication, PK avail.	**Clinical evidence** Effic. or MAD doses in desired indication; PK avail. is mixed	**Clinical evidence** Non-target indication, PK avail is mixed	**Clinical evidence** None

Balancing valency, affinity, half lives with dosing schedule

					Schedule:	SC Q4W				SC Q6W				SC Q8W			
					Valency:	1 + 1	1 + 2	2 + 1	2 + 2	1 + 1	1 + 2	2 + 1	2 + 2	1 + 1	1 + 2	2 + 1	2 + 2
Molecule	Target Pair	Modality	Lead indication	SoA	Half life												
X					10d												
					20d												
					30d												
					42d												

Color key (i.e., darker = better):

- Feasible with **both Kds ≥ 100 nM**
- Feasible with **one** Kd < 100 nM
- Feasible with **both** Kds **< 100 nM**
- Not feasible

Simulations across a portfolio of drug concepts can enable prioritization based on likelihood that the drug can achieve efficacy with desired dosing regimen and guide design

EFA

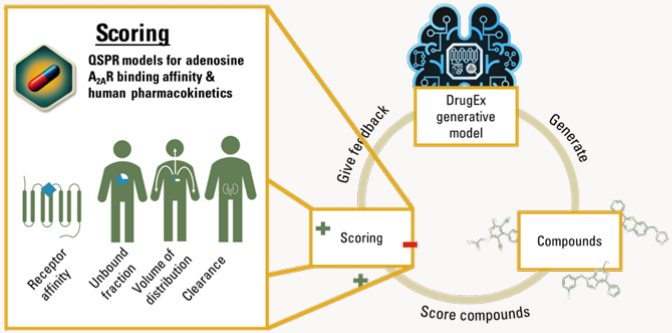
1. Quantifies Developability
2. Guides Design
3. Ranks Clinical Confidence in Rationale

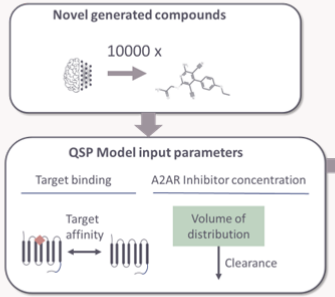
EFA requires no *in vivo* animal data, no *in vitro data*, no compounds

From EFA to QSP-Enabled Generative Drug Design

Integrating Pharmacokinetics and Quantitative Systems Pharmacology Approaches in Generative Drug Design

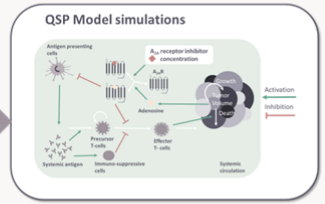
Helle W. van den Maagdenberg, Jikke de Mol van Otterloo, J. G. Coen van Hasselt, Piet H. van der Graaf, and Gerard J. P. van Westen*

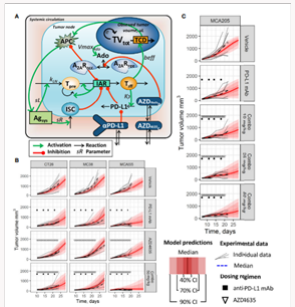




Evaluation of Combination Strategies for the $A_{2A}R$ Inhibitor AZD4635 Across Tumor Microenvironment Conditions *via* a Systems Pharmacology Model

Veronika Voronova[1*], Kirill Peskov[1,2], Yuri Kosinsky[1], Gabriel Helmlinger[3], Lulu Chu[3], Alexandra Borodovsky[3], Richard Woessner[4], Kris Sachsenmeier[4], Wenlin Shao[3], Rakesh Kumar[3], Gayle Pouliot[4], Melinda Merchant[4], Holly Kimko[3] and Ganesh Mugundu[3]

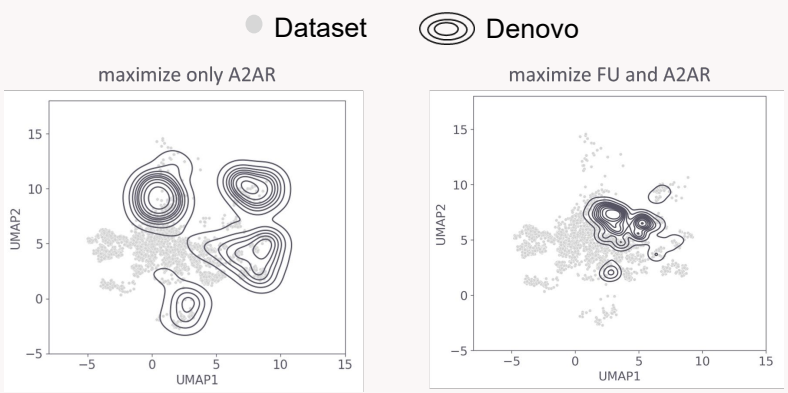




- Affinity, PK and clinical efficacy for 10,000 *denovo* compounds
- Safety could be integrated seamlessly

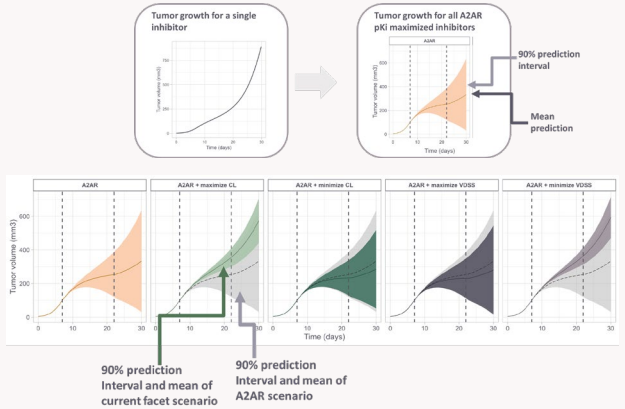
doi:10.1021/acs.jcim.5c00107

From EFA to QSP-Enabled Generative Drug Design

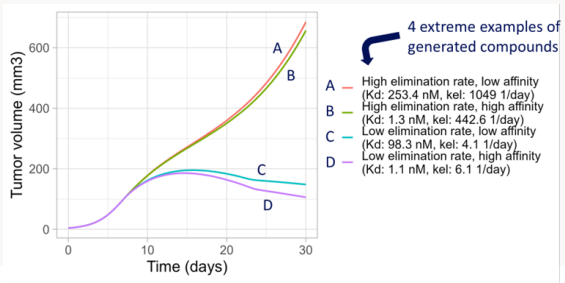


QSP

N=10,000



Simultaneously optimizing Affinity and PK constrains chemical space



doi:10.1021/acs.jcim.5c00107

Certara has the largest library of validated EFA/QSP platform models in the industry

Disease Based Platforms

- Immuno-Oncology
- Neurology (AD, PD, ALS,ect.)
- Immunogenicity
- Inflammatory bowel disease

Modality Based Platforms

TCE | ADC | Biotherapeutics | Gene Therapy | Protein Degraders

Certara IQ

Intelligent QSP

Scale Ability to support the entire R&D portfolio

Speed Move at the speed of portfolio & regulators

Consistent High-quality for every project

Trusted Stakeholders understand model

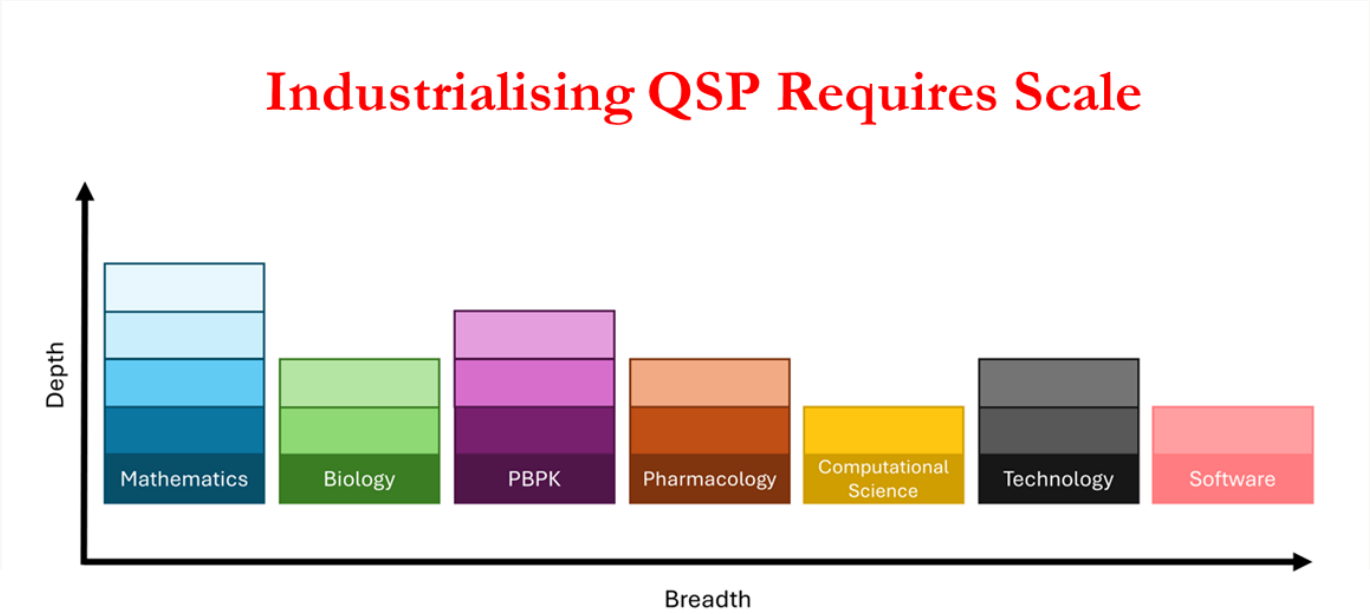
Collaborative Engage diverse stakeholders

Essential Working with industry and global agencies to make QSP *digital evidence* in filings

CERTARA

Why is EFA not used in every program?

Why would you need support from Certara?



Certara Applied BioSimulation (ABS): The Industry's leading QSP Center of Excellence

70+	700+	275+	350+
QSP Scientists	Projects	Clients	Combined Years of Experience

CERTARA

piet@certara.com