CERTAINTY DISCOVERY

CERTARA | Chemaxon

Enabling AI-driven Modeling and Simulation-based Decision making in Discovery Towards Increased Clinical Drug Candidate Success

Robert Aspbury

Certara

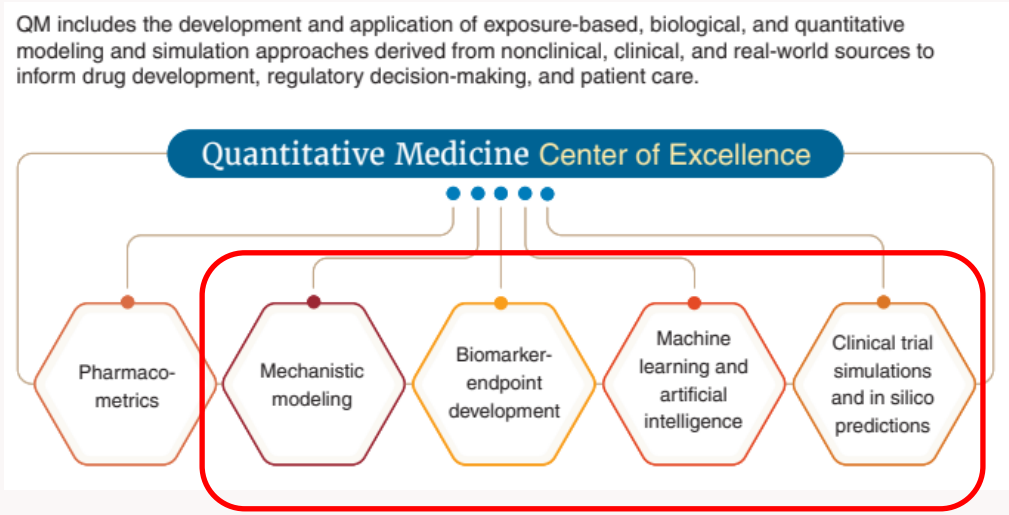
President of Certara's Predictive Technologies

Enabling AI-Driven Modelling and Simulation-Based Decision Making in Discovery Towards Increased Clinical Drug Candidate Success

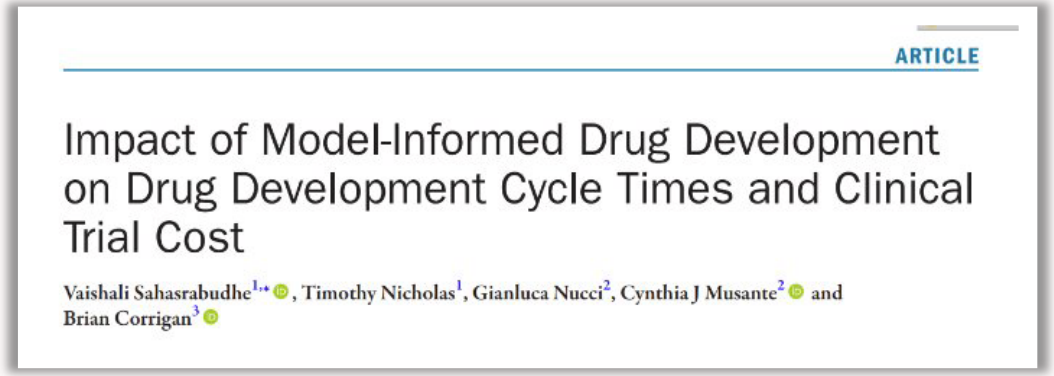
Rob Aspbury
President Certara Predictive Technologies

CERTARA

Model-Informed Drug Development (MIDD) - *Biosimulation*



- The establishment of MIDD has been an *Evolution* over decades, generating incremental Efficiencies
- The culmination of years of scientific innovation has made quantitative medicine a reality
  - Clinical Trial Waivers
  - Embedded throughout the drug development process, supporting internal decision making


ARTICLE

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]

MIDD facilitated decision making in EVERY development program

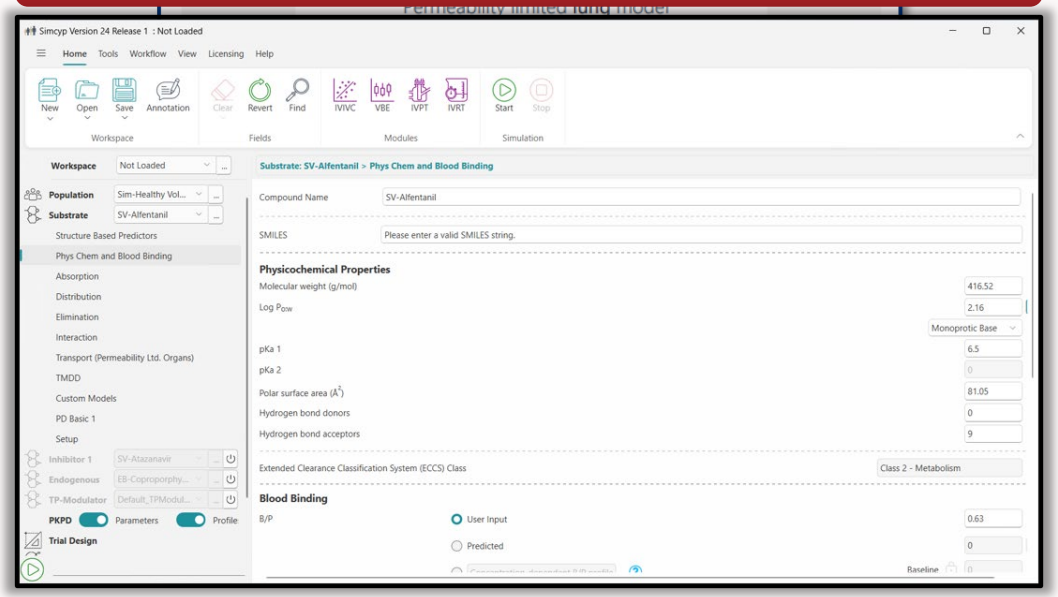
$5M and 10 months savings per program

Model Informed Drug Development (MIDD)

Mechanistic modeling approaches are able to simulate drug exposure (pharmacokinetics), target engagement, pharmacology modulation, efficacy and toxicity

Physiologically-based pharmacokinetic (PBPK) modeling

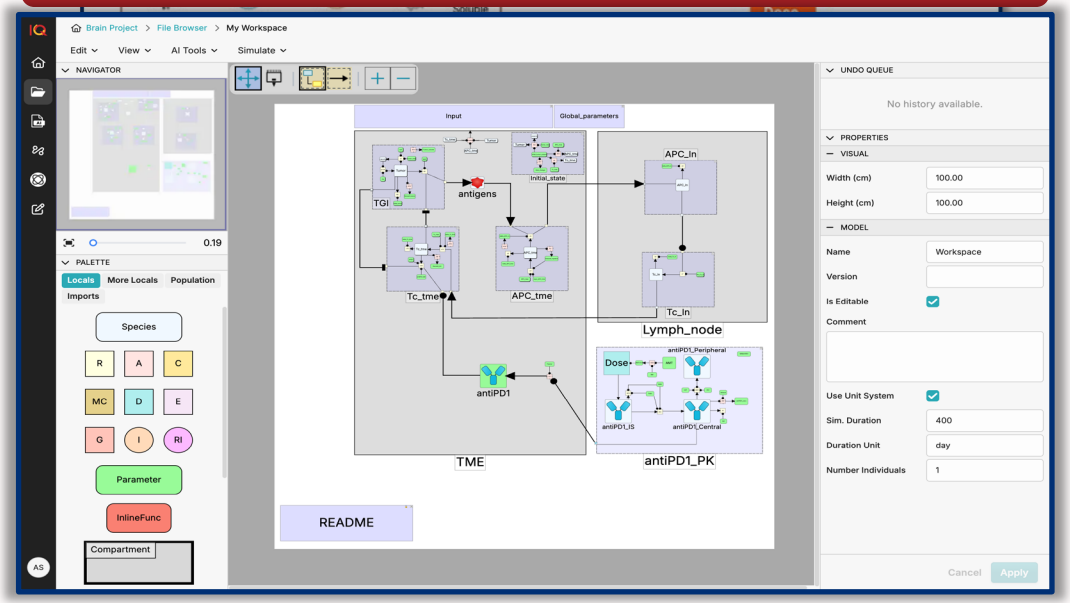
Simcyp Simulators



Commonly used to address **PK**-related questions
(What the body does to the drug?)

Quantitative Systems Pharmacology (QSP) modeling

Certara IQ (A.I. Enabled)



Commonly used to address **PD**-related questions
(What the drug does to the body?)

Use of M&S in support of regulatory submissions is well established

- Generating supporting data, supporting label claims, and obtaining trial waivers etc

European Journal of Pharmaceutical Sciences 200 (2024) 106838

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

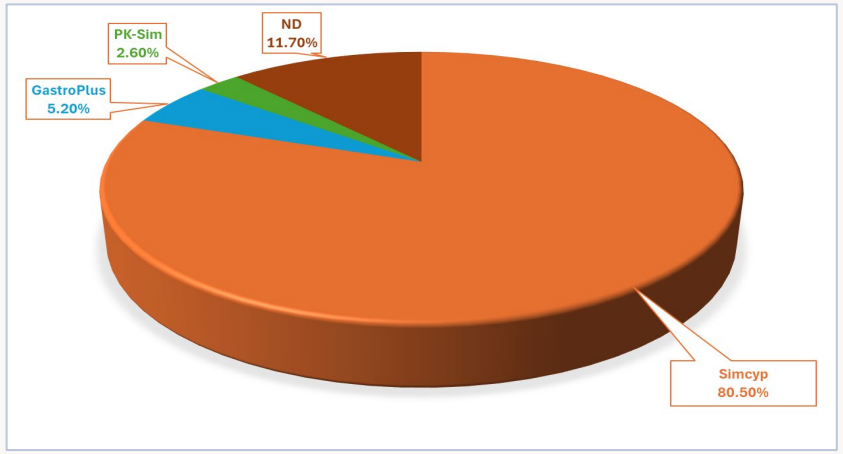
journal homepage: www.elsevier.com/locate/ejps

ELSEVIER

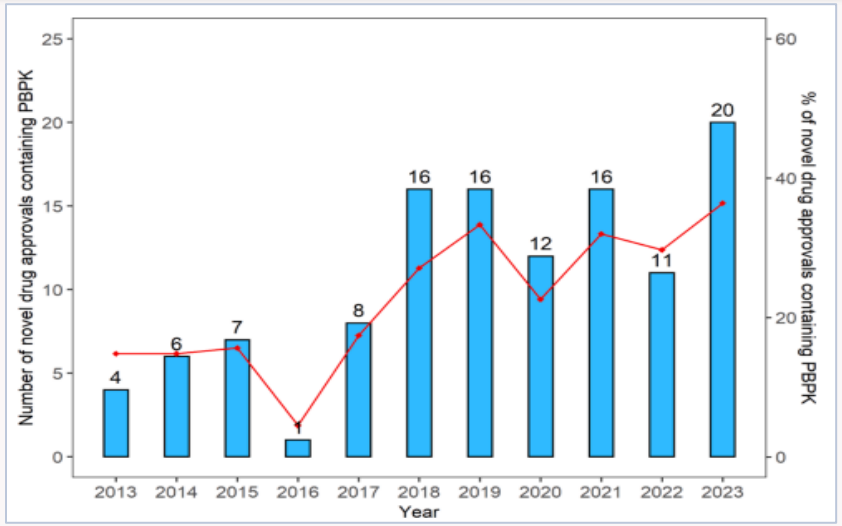
Review

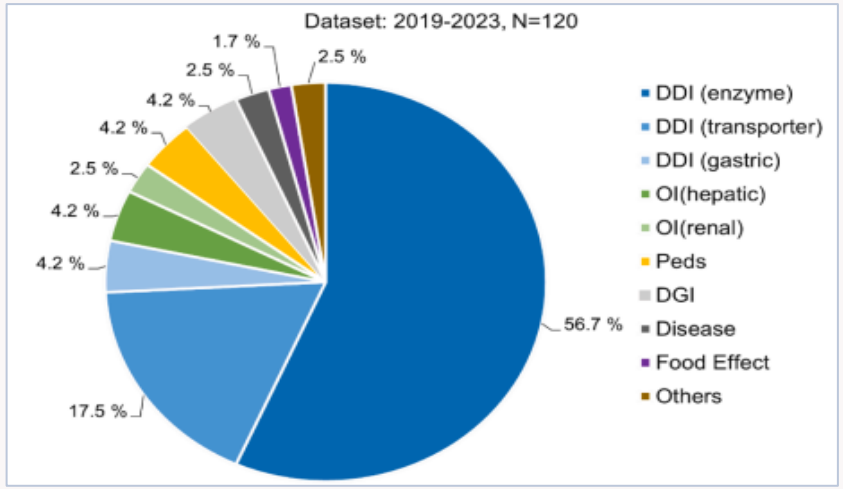
Application of physiologically based pharmacokinetic modeling of novel drugs approved by the U.S. food and drug administration

Zexu Sun [a,b,c], Nan Zhao [d], Xia Zhao [d], Ziyang Wang [d], Zhaoqian Liu [b,e,f,*], Yimin Cui [a,c,g,*]



Simcyp has been utilized in more than 80% of FDA-approved drug applications involving PBPK modelling (2019-2023)





- Many DDIs use cases
- Increasingly used to inform dose in paediatrics, renally/hepatically impaired patients and to determine food effects

PBPK Modeling Regularly Used to Support Label Claims

125+ novel drugs used the Simcyp Simulator in lieu of clinical studies

ONCOLOGY

AbbVie	Venclexta *(venetoclax)*
Agios	Tibsovo *(ivosidenib)*
Amgen	Blincyto *(blinatumomab)*
Amgen	Lumakras *(sotorasib)*
Ariad	Alunbrig *(brigatinib)*
Ariad (Takeda)	Iclusig *(ponatinib)*
AstraZeneca	Calquence *(acalabrutinib)*
AstraZeneca	Lynparza *(olaparib)*
AstraZeneca	Tagrisso *(osimertinib)*
AstraZeneca	Truqap® *(capvasertib)*
Beigene	Brukinsa *(zanubrutinib)*
Biohaven	Nurtec *(rimegepant)*
BluePrint Medicines	Ayvakit *(avapritinib)*
Celgene	Inrebic *(fedratinib hydrochloride)*
Daiichi Sankyo	Turalio *(pexidartinib)*
Daiichi Sankyo	Ezharmia *(valmetostat tosilate)*
Daiichi Sankyo	Vanflyta® *(quizartinib dihydrochloride)*
Daiichi Sankyo	Datroway *(datopotamab deruxtecan-dlnk)*
Deciphera	Qinlock *(ripretinib)*
Eisai	Lenvima *(lenvatinib)*
EMD Serono	Tepmetko *(tepotinib hydrochloride)*
Genentech	Alecensa *(alectinib)*
Genentech	Cotellic *(cobimetinib)*
Genentech	Gavreto® *(pralsetinib)*
Genentech	Polivy *(polatuzumab vedotin-piiq)*
Genentech	Rozlytrek *(entrectinib)*
GSK	Zejula *(niraparib)*
Incyte	Pemazyre *(pemigatinib)*
Janssen	Balversa *(erdafitinib)*
Janssen	Lazcluze *(lazertinib)*
Janssen	Erleada *(apalutamide)*
Lilly	Retevmo *(selpercatinib)*
Lilly	Verzenio *(abemaciclib)*
Loxo	Jaypirca *(pirtobrutinib)*
Loxo Oncology	Vitrakvi *(larotrectinib)*
Menarini/Stemline	Orserdu *(elacestranto)*
Mirati	Krazati *(adagrasib)*
Novartis	Farydak *(panobinostat)*
Novartis	Kisqali *(ribociclib succinate)*
Novartis	Scemblix *(asciminib)*
Novartis	Odomzo *(sonidegib)*
Novartis	Vijoice *(alpelisib)*
Novartis	Rydapt *(midostaurin)*
Novartis	Tabrecta *(capmatinib)*

Oncology continued:

Novartis	Zykadia *(ceritinib)*
Novartis	Jakavi *(ruxolitinib)*
Nuvation Bio	Ibtrozi *(taletrectinib)*
Pfizer	Daurismo *(glasdegib)*
Pfizer	Ibrance® *(palbociclib)*
Pfizer	Bosulif *(bosutinib)*
Pfizer	Lorbrena *(lorlatinib)*
Pharmacyclics	Imbruvica *(ibrutinib)*
PumaDiabetic	Nerlynx® *(neratinib)*
Sanofi	Jevtana *(cabazitaxel)*
Seattle Genetics	Tukysa *(tucatinib)*
Servier	Voranigo *(vorasidenib)*
Spectrum	Beleodaq *(belinostat)*
Springworks	Ogsiveo® *(nirogancent)*
Syndax Pharmaceuticals	Revuforj *(revumenib)*
Takeda	Exkivity *(mobocertinib)*
Takeda	Fruzaqla® *(fruquintinib)*
Taiho	Lytgobi *(futibatinib)*
Verastem	Copiktra *(duvelisib)*

RARE DISEASE

Agios	Pyrukynd *(mitapivat)*
AkaRx (Eisai)	Doptelet *(avatrombopag maleate)*
AstraZeneca	Koselugo *(selumetinib)*
Aurinia	Lupkynis *(voclosporin)*
Genentech	Enspryng *(satralizumab)*
Genentech	Evrysdi *(risdiplam)*
Global Blood Therapeutics	Oxbryta *(voxelotor)*
Intercept	Ocaliva *(obeticholic acid)*
Ipsen	Sohonus® *(palovarotene)*
Kadmon	Rezurock *(belumosudil)*
Merck	Welireg *(belzutifan)*
Mirum	Livmarli *(maralixibat)*
Mitsubishi Tanabe	Dysval *(valbenazine)*
Novartis	Isturisa *(osilodrostat)*
Peloton/Merck	Welireg *(belzutifan)*
PTC Therapeutics	Emflaza *(deflazacort)*
Sanofi Genzyme	Cerdelga *(eliglustat tartrate)*
Soleno Therapeutics	VYKAT™ XR *(diazoxide choline)*
Sun Pharmaceutical Inc.	Leqselvi *(deuruxolitinib)*
Travere	Filspari *(sparsentan)*
Vertex	Symdeko *(tezacaftor/ivacaftor)*
Vertex	Trikafta *(elexacaftor/ivacaftor/tezacaftor)*

CENTRAL NERVOUS SYSTEM

AbbVie	Rinvoq *(upadacitinib)*
AbbVie	Qulipta *(atogepant)*
Alkermes	Aristada *(aripiprazole lauroxil)*
Alkermes	Lybalvi *(olanzapine/samidorphan)*
Eisai	Dayvigo *(lemborexant)*
Idorsia	Quviviq *(daridorexant)*
Janssen	Ponvory *(ponesimod)*
Kyowa Kirin	Nourianz *(istradefylline)*
Lilly	Reyvow *(lasmiditan succinate)*
Novartis	Mayzent *(siponimod fumaric acid)*
Novartis	Vanrafia *(atrasentan)*
Pfizer	Zavzpret *(zavegepant)*
UCB	Briviact *(brivaracetam)*
Vertex	Journavx *(suzetrigine)*

INFECTIOUS DISEASE

Gilead	Veklury *(remdesivir)*
GSK	Blujepa *(gepotidacin mesylate)*
Janssen	Olysio *(simeprevir)*
Merck	Pifeltro *(doravirine)*
Merck	Prevymis *(letermovir)*
Nabriva	Xenleta *(lefamulin acetate)*
Novartis	Egaten *(triclabendazole)*
Pfizer	Paxlovid® *(nirmatrelvir, ritonavir)*
Tibotec	Edurant *(rilpivirine)*
ViiV	Cabenuva Kit *(cabotegravir/rilpivirine)*

GASTROENTEROLOGY

AstraZeneca	Farxigo *(dapaglifoxin)*
AstraZeneca	Movantik *(naloxegol)*
Helsinn	Akynzeo *(fosnetupitant/palonosetron)*
Phathom	Voquezna TriplePak *(vonoprazan/amoxicillin/clarithromycin)*
Shionogi	Symproic *(naldemedine)*
Shire	Motegrity *(prucalopride)*

CARDIOVASCULAR

Actelion (J&J)	Opsumit *(macitentan)*
BMS	Camzyos *(mavacamten)*
BridgeBio	Attruby *(acoramidis)*
Johnson & Johnson	Xarelto *(rivaroxaban)*
Pfizer	Revatio *(sildenafil)*

ENDOCRINE

AbbVie	Orilissa *(elagolix)*
Astellas	Veozah® *(fezolinetant)*
Esperion	Nexetol *(bempedoic acid)*
Janssen	Invokana *(canagliflozin)*
Lilly	Olumiant *(baricitinib)*
Lilly	Mounjaro *(tirzepatide)*
Merck	Steglatro *(ertugliflozin)*

OTHER

Galderma	Aklief *(trifarotene)*
Gilead	Livdelzi *(seladelpar)*
Takeda	Livtencity *(maribavir)*
Vertex	Alyftrek *(vanzacaftor, tezacaftor, and deutivacaftor)*

Updated July 2025

CERTARA

PBPK modeling used to predict "complex DDI" scenarios

- Recently we are seeing many more projects with complex DDI scenarios
  - For example, where the drug is a substrate for CYP3A4, an inhibitor of CYP3A4 (competitive and time dependent) and an inducer of CYP3A4
  - Time dependent non-linear PK and complex DDI scenarios
  - DDI liability may be different on single dose versus multiple dose
  - Extensive use of itraconazole, rifampicin and midazolam studies to build and verify the models
- PBPK modelling is really the only option to understand the complexity and is being used successfully in lieu of DDI studies

The Rise of QSP

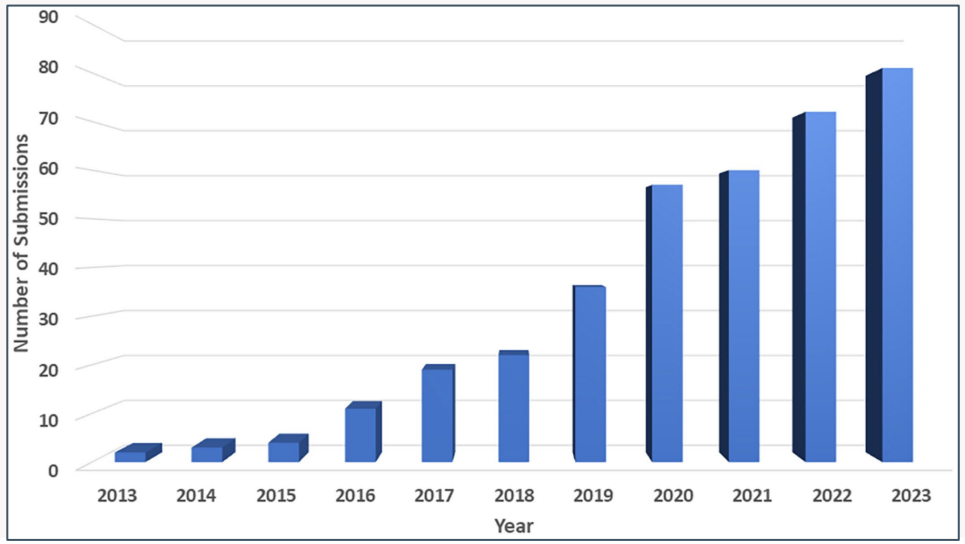
DOI: 10.1002/psp4.13208

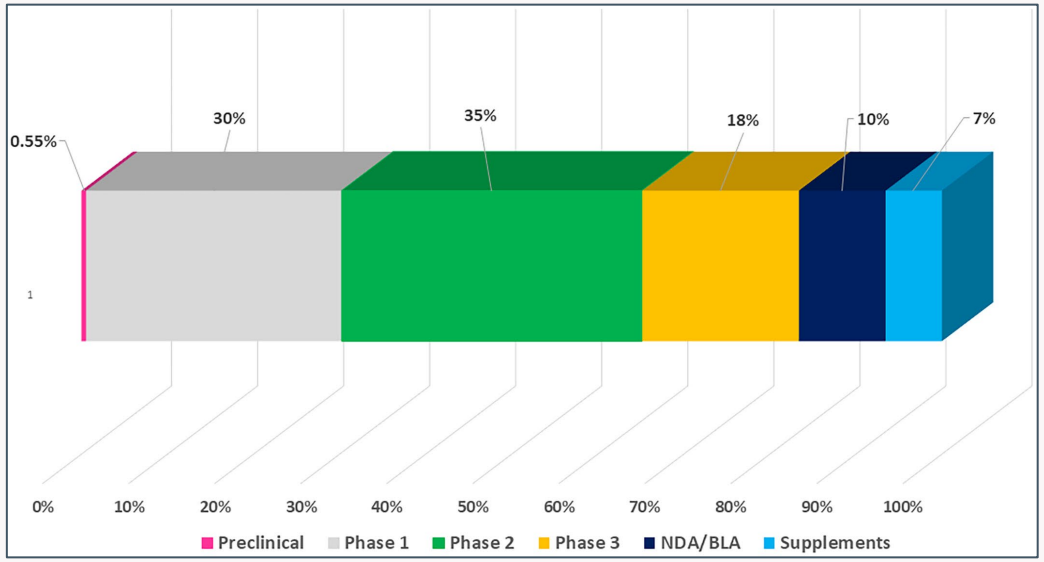
ARTICLE

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

Yearly trend of quantitative systems pharmacology submissions from 2013 to 2023





- Majority (65%) of QSP submissions were for Phase I and Phase II
- NDA and BLA submissions plus post-approval submissions (supplements) were 17% of the total submissions

CERTARA

QSP Modeling for Human Dose Prediction

ICHNOS GLENMARK INNOVATION

nature cancer

Article https://doi.org/10.1038/s43018-024-00821-1

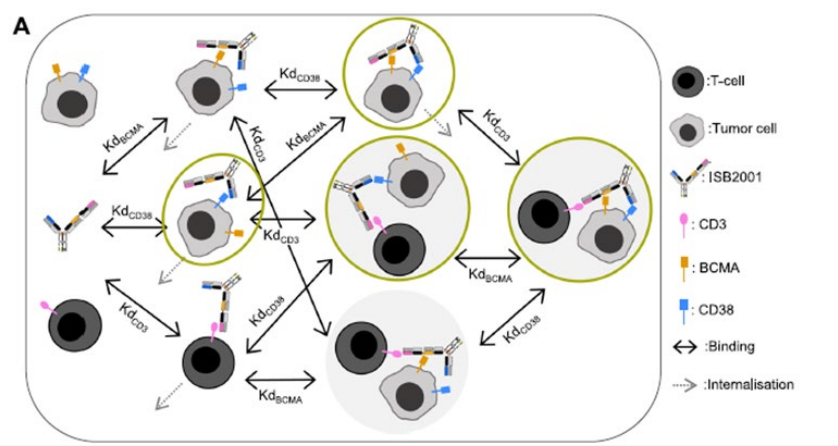
ISB 2001 trispecific T cell engager shows strong tumor cytotoxicity and overcomes immune escape mechanisms of multiple myeloma cells

Background/Challenge

- ISB2001 is a first-in-class, tri-specific mAb CD3 T-cell engager co-targeting BCMA and CD38 for multiple myeloma
- Conventional "MABEL"* approaches typically lead to very low FIH starting dose
- ISB 2001 lacks cross-reactivity to monkey -> no preclinical studies conducted
- Animal models may not translate to complex patient pathophysiology

Solution

- QSP modeling to generate human predictions based on preclinical *in vitro* data
- Calibrated/validated with competitor clinical data (teclistamab)



Result and Impact

- QSP allowed for 50-100x higher FIH starting dose compared to conventional MABEL
- Approved by multiple regulatory agencies
- Model predicts superiority (lower dose) compared to teclistamab
- QSP model predictions were clinically validated

"Despite the absence of monkey PK and toxicology data, this QSP-guided approach successfully predicted an optimal FIH dose, clinical PK, safety and efficacy, while minimizing patient exposure to non-therapeutic doses."

CERTARA

*MABEL = minimal anticipated biological effect level

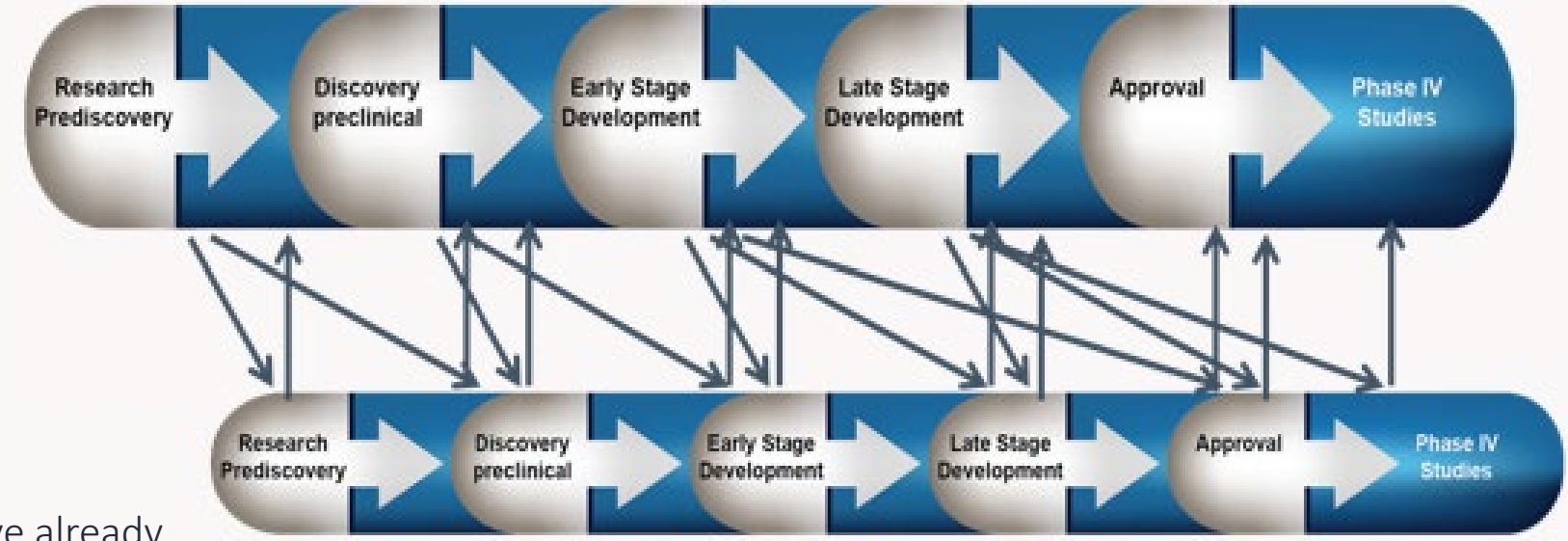
Biosimulation Embedded Throughout Development Programs

The commercial value of “Regulatory Wins” is compelling but arguably, making modelling integral to decision making throughout the drug development cycle is where the magic happens

(PBPK, QSP, QSTS, PK/PD, popPK)

Virtual

Drug development program



Actual

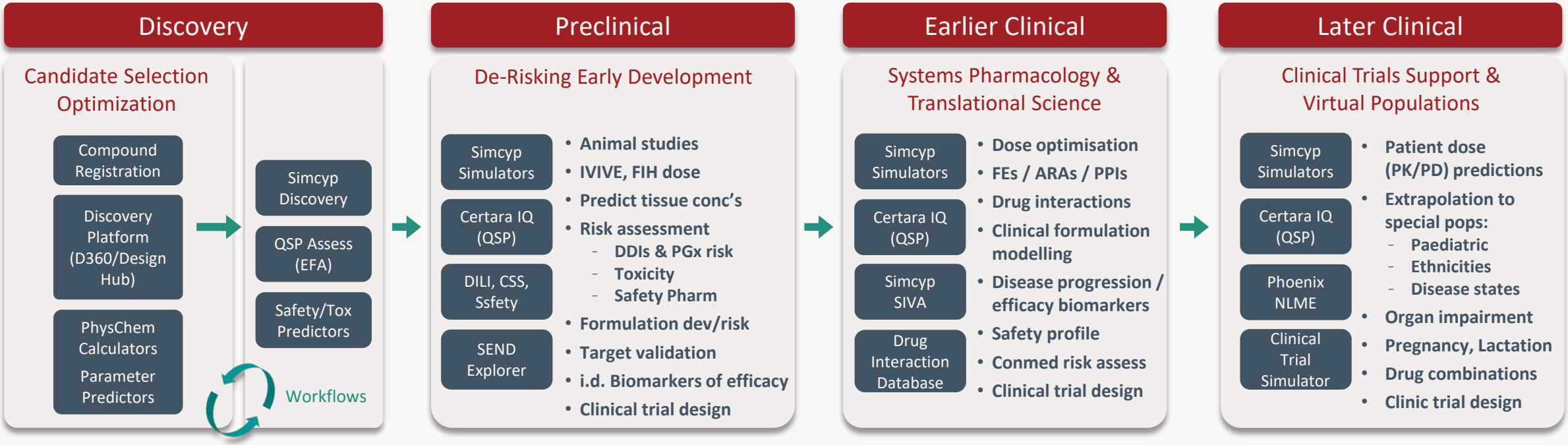
Drug development world

- Taking advantage of events that have already happened in the virtual world
- Ability to move faster, and more predictably and reliably

CERTARA

Certara MIDD Platform

Data Integration & Predictive Analytics Delivering Certainty Across Drug Development



"In-Silico Profile" concept

- Unique library of data which defines/characterises a compound and provides input parameters for in-silico predictions
- Compound Profile expands and transform over time as experimental data is generated and accumulated
- Standardised data formats allow predictive models to be run as automated workflows across large numbers of compounds and test scenarios

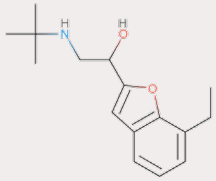
CERTARA

Integrating Simcyp and Database workflows

Simcyp Discovery (PBPK software)

Chemical Structure SMILES String

CCC1=CC=CC2=C1OC(=C2)C(CNC(C)(C)C)O



Drug Data

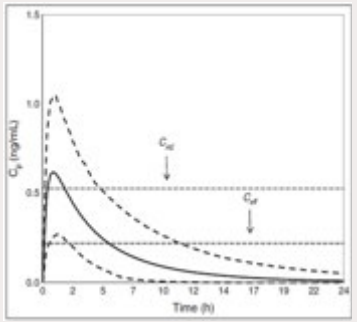
Simcyp "Predictor Platform"
MW, LogP, LogD, HLB, PKa, PSA, LogS, CLint, fu, BP

Trial & Physiology Data

Single or Multiple Dose, Oral Formulatio
"Standard Healthy Human"

SIMCYP DISCOVERY (PBPK Software)

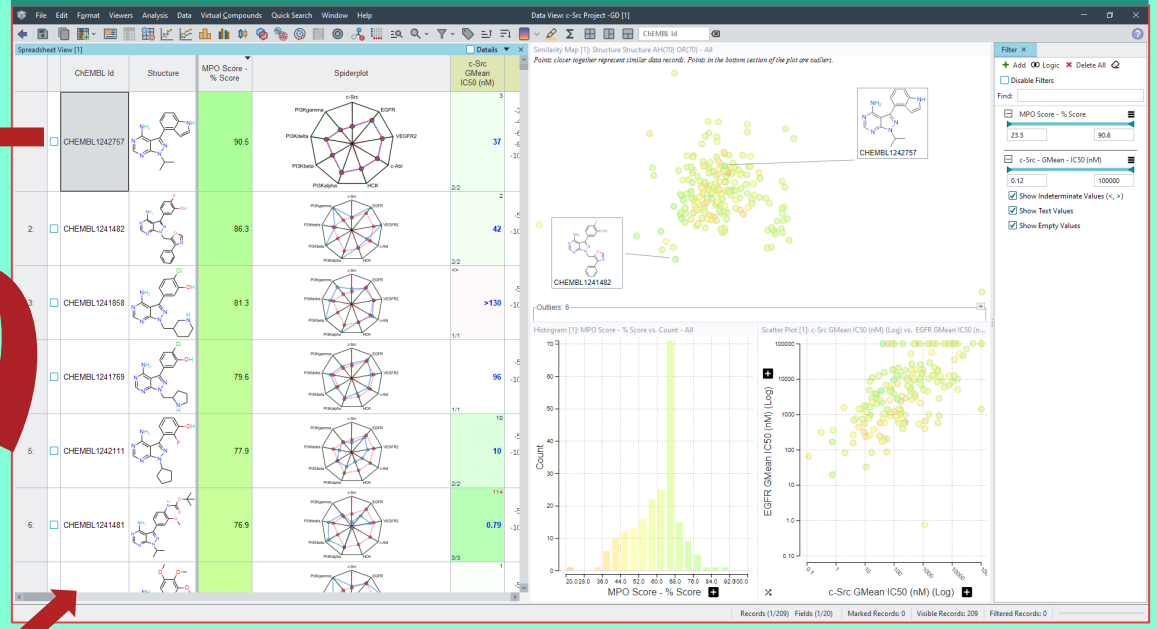
Pharmacokinetic predictions in animals / humans



Cmax
UAC

DISCOVERY SOFTWARE

D360

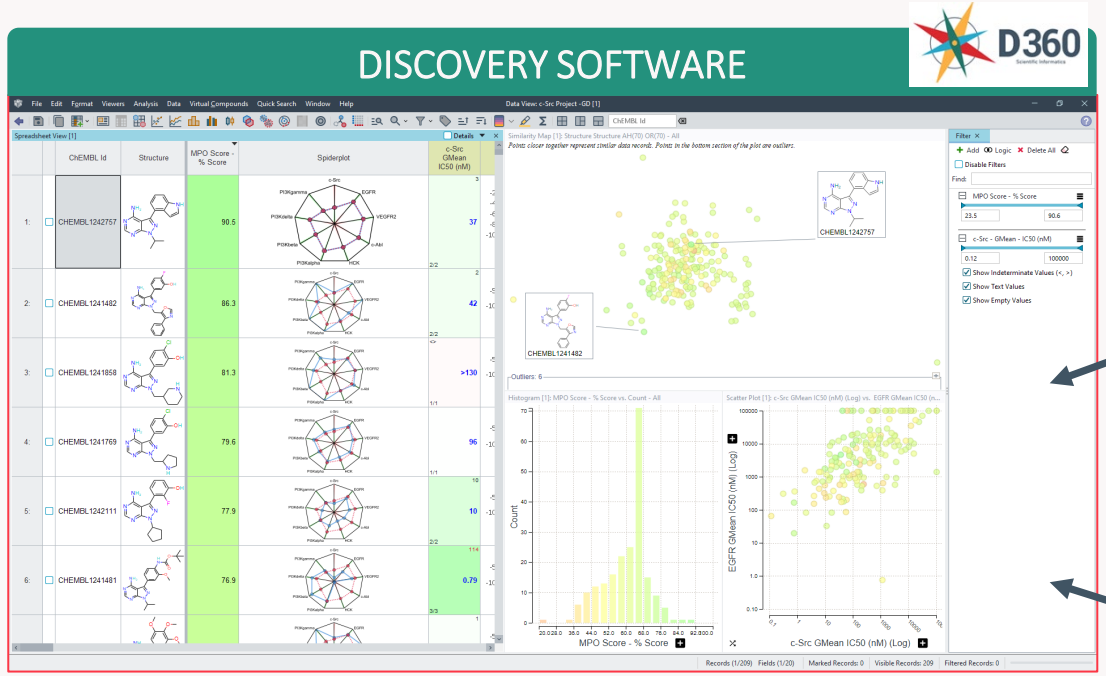


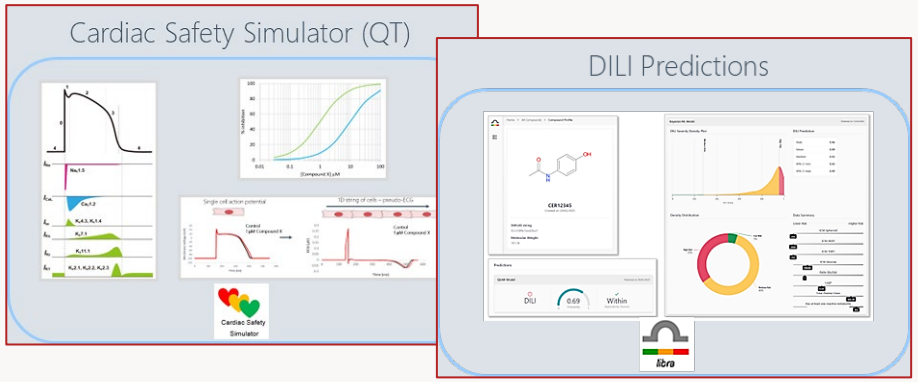
Enhanced, Streamlined Candidate Selection!

- Cloud (SaaS) based version of Simcyp Discovery, enables high volume, automated ('batch') workflows for large datasets
- Supports high-throughput analysis

CERTARA

Other Example Workflows

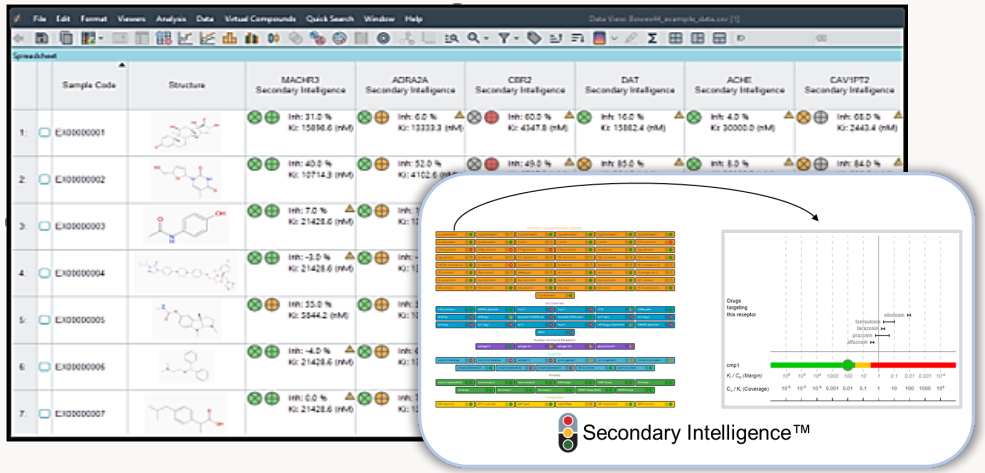




Input parameters required to generate early DILI / cardiac safety risk predictions collected early in Discovery

(data also used to improve/train models)

- Secondary intelligence is a risk assessment tool based on secondary pharmacology assay data
- Risk can be displayed in terms of traffic lights
- Useful in prioritizing compounds using D360's ability to assess compounds with multi-parameter scoring



CERTARA

Early Feasibility Assessment (EFA)using QSP Modeling

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?

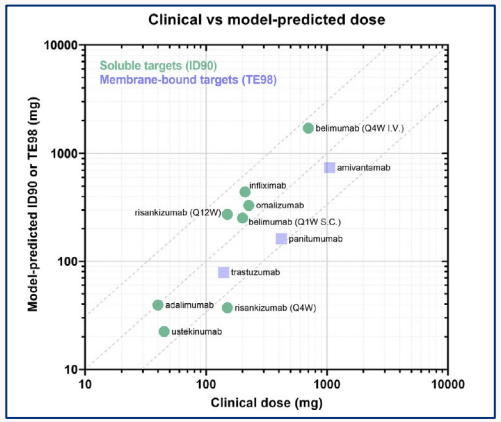
What are the required drug properties to achieve the desired pharmacology at feasible doses?

FIT FOR PURPOSE

Aligned with drug discovery requirements and cycle times

- Consistent, reliable
- Turnaround days-weeks
- EFA requires no *in vivo* animal data

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

CERTARA

AZ Retrospective Review (July 2025)

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

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

Rasmus Jansson-Löfmark [1,*], Markus Fridén [2,5], Lassina Badolo [2], Christine Ahlström [1], Ian Gurrell [4], Menelas N. Pangalos [6], Rhys DO Jones [3,*]

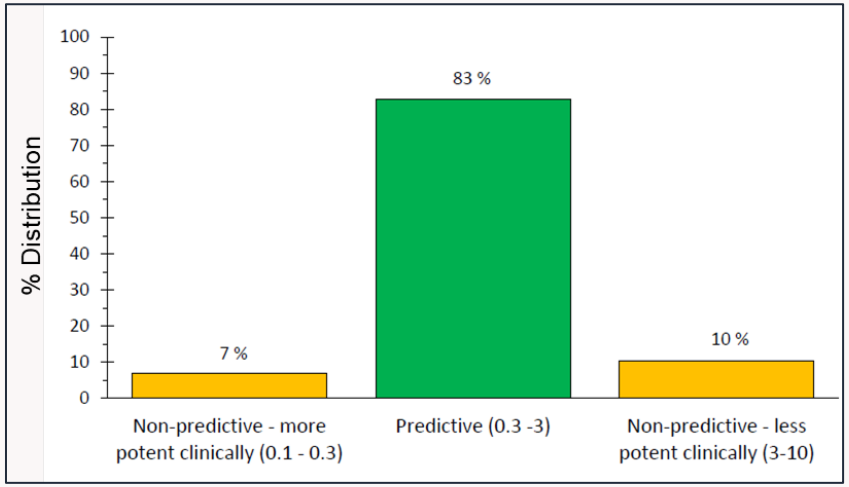
(reviewed compounds nominated as candidates 2007-2019)

- Right target
- Right tissue/exposure
- Right patient
- Right safety
- Right commercial

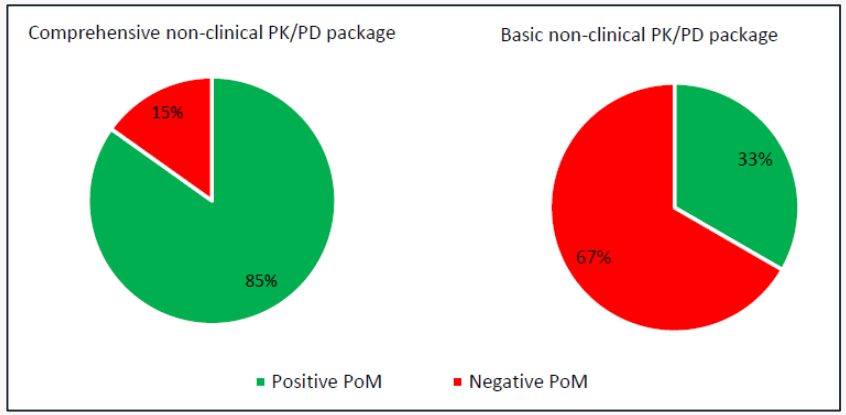
PBPK / QSP / ER modelling can be used define the level of target engagement expected to be necessary for clinical activity, the required exposure profile and the required dose to achieve this

Basic translational PK/PD package - relied solely on in-vitro potency without considering prior knowledge of the target, or consideration for local tissue exposure

Comprehensive translational PK/PD package – projected clinical efficacy used a biomarker (clinical PD) model with quantitative assessment of PK/PD translation



Translational PK/PD modelling with non-clinical datasets can successfully predict E/R for target engagement in humans (83% of compounds had drug exposure-response within a threefold prediction accuracy)



Projects with robust PK/PD packages achieved an 85% success rate in PoM compared with 33% for those with basic packages

CERTARA

Genentech

- Use of PBPK to prioritise molecules with the desired PK profiles
- Physchem and in-vitro data only, with no compound specific fitting (with in-vivo data)

Journal of Medicinal Chemistry

pubs.acs.org/jmc Article

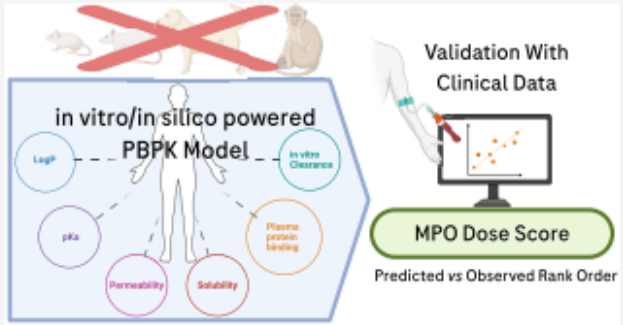
Human-Focused Multiparameter Optimization Scores for Rank Ordering Compounds during Early Drug Discovery: Validation of PBPK Models Based on Clinical PK Data

Yanran Wang,*,⊥ Wenyi Wang,⊥ Fabio Broccatelli, Jane R. Kenny, Matthew R. Wright, Jon Sorenson, and Prashant Desai*

Cite This: https://doi.org/10.1021/acs.jmedchem.5c01707 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Physiologically based pharmacokinetic (PBPK) models are increasingly used in drug discovery to prioritize compounds that meet the desired pharmacokinetic (PK) profiles. We developed a generalized PBPK model using only early discovery *in vitro* data and validated it across 18 Genentech compounds without compound-specific fitting. The model effectively rank-ordered compounds based on hypothetical PK drivers of pharmacodynamics, including minimum and maximum unbound concentrations (C_{minu} and C_{maxu}) and unbound area under the curve (AUCu). In contrast, ranking based on any single *in vitro* parameter alone was less predictive. Additionally, the model provided reasonable predictions of clinical PK parameters such as apparent clearance, volume of distribution, Cmax, AUCinf, and full concentration−time profiles. This work represents the first validation of clinical PK prediction using early discovery data in a bottom-up manner and demonstrates the potential of PBPK modeling as a multiparameter optimization tool to guide the selection and optimization of compounds in the early stages of drug discovery.



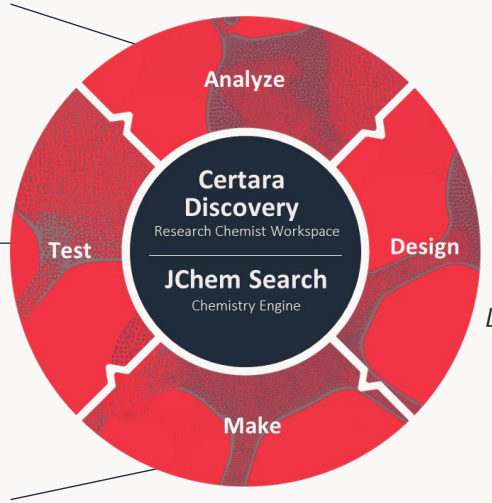
In-silico Models Can Enhance The Design Process in Discovery

Multiparameter Optimization

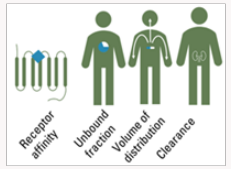
Decide if the compound met the objectives

Run the compound through multiple assays

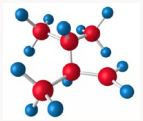
Synthesize designed compound



In-silico profile

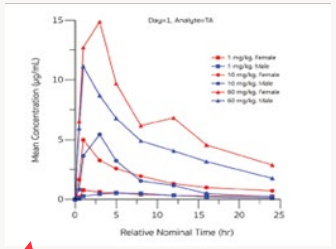


KD	CMax	AUC	CL	Fu	PPB
X	X	X	X	X	X

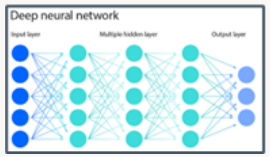


Determine what compound to make next

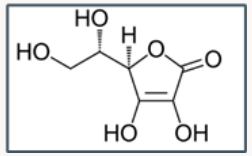
In-silico optimisation



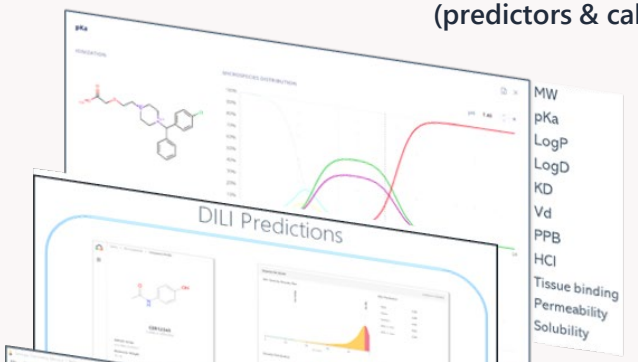
Generate Novel Compounds

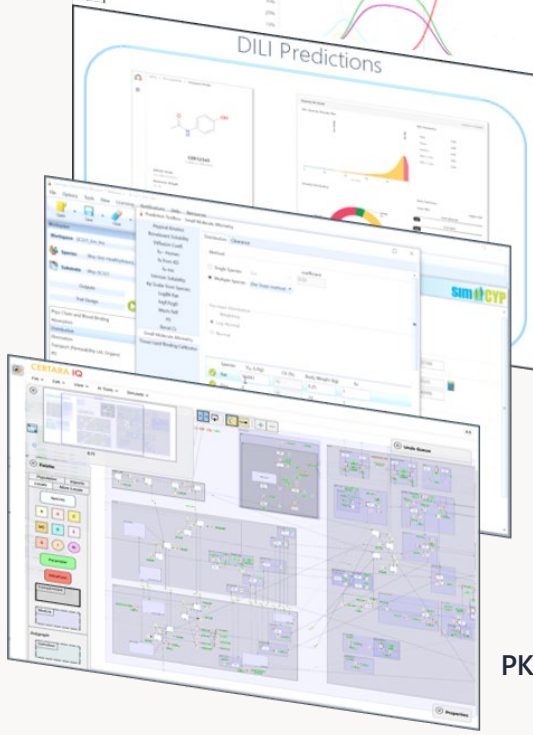


10,000s x



Model Parameters (predictors & calculators)





Safety/Tox Profile (DILI)

PK Profile (Simcyp)

PK/PD Profile (IQ)

CERTARA

Introducing Certara "Nexus"

Certara Cloud / Admin

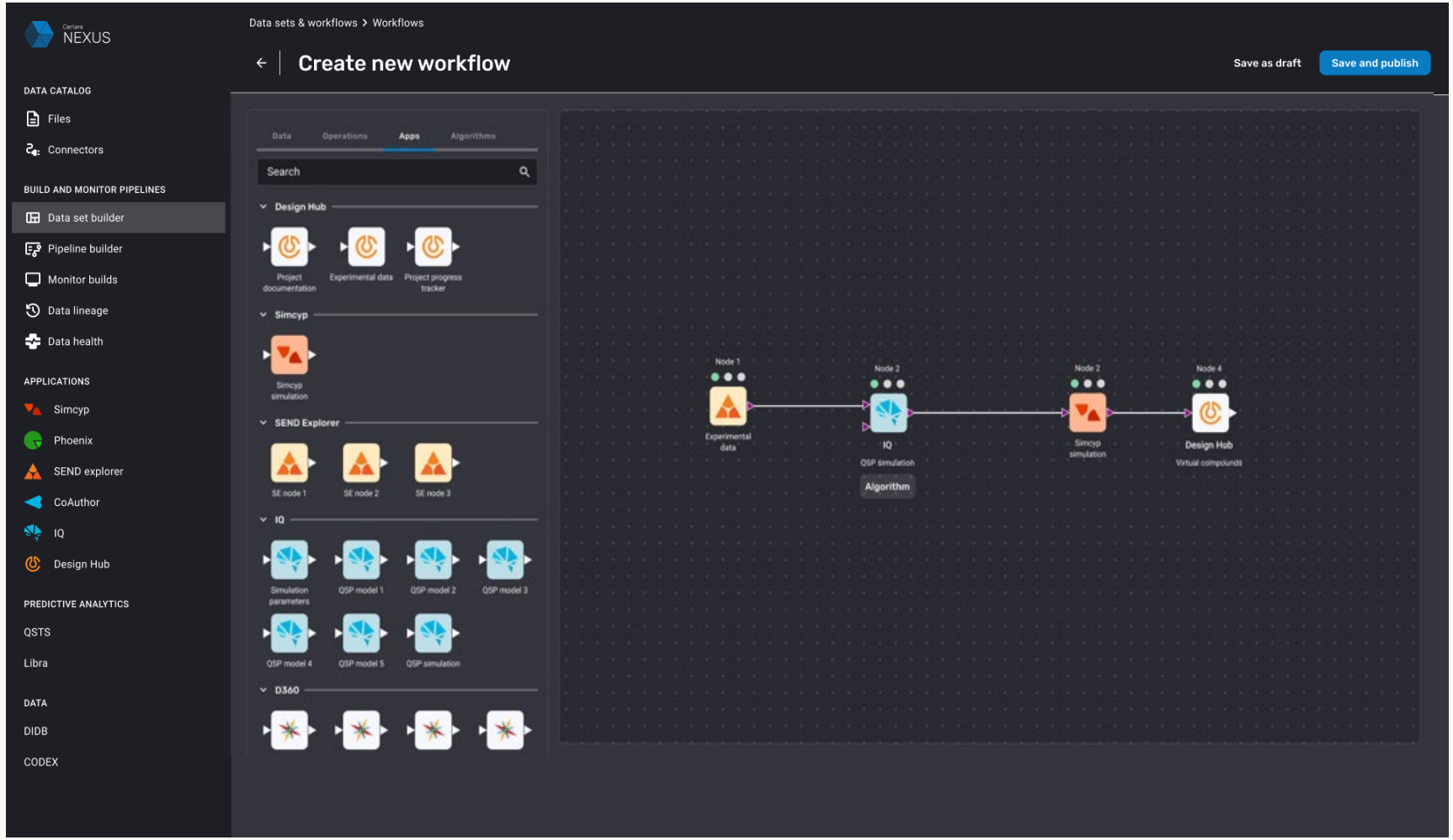
Certara Layar Software

- Creates an Integrated Data Catalog
- Security, privileging, client-specific data integration
- Configurable LLM model architectures
- Integration of structured and unstructured data
- AI For Automated Structured Data Mapping
- Supports Multi-Agent AI Frameworks

Certara Software

- Software Applications
- Data Engines
- Predictive Anlaytics Tools
- Proprietary Data Sets

Integrated Third Party Software, Applications, Data Sets



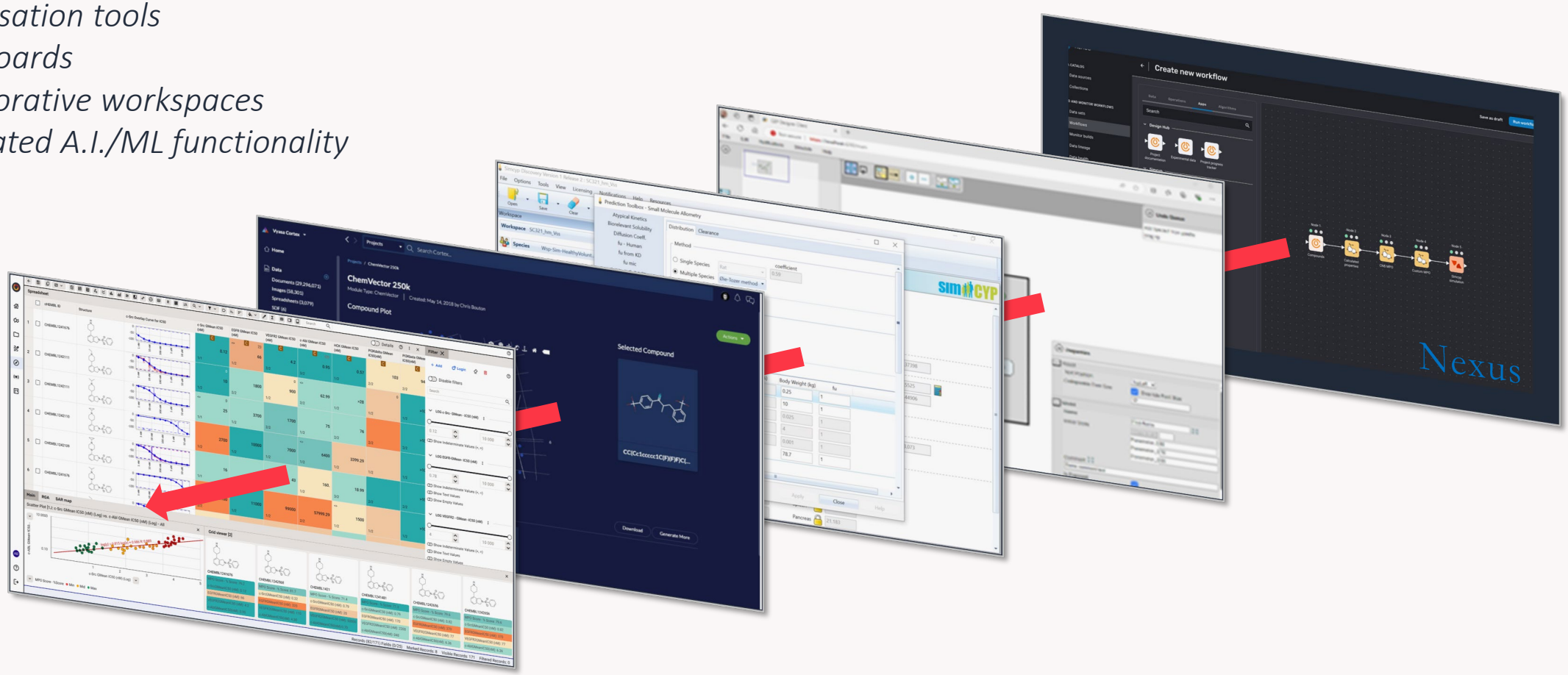
Certara Elastic Compute

CERTARA

Certara MIDD Platform

Pairing front-end modelling/analytics software with a back-end data orchestration layer

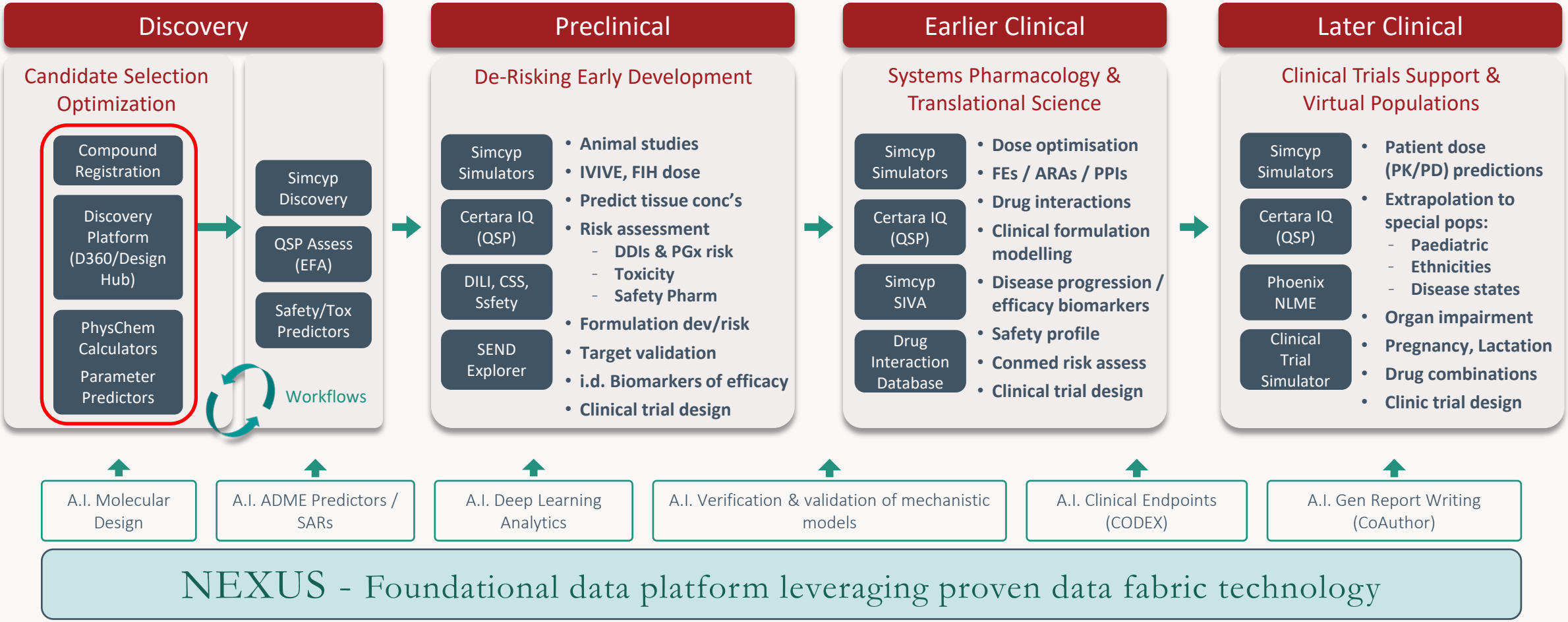
- *Visualisation tools*
- *Dashboards*
- *Collaborative workspaces*
- *Integrated A.I./ML functionality*



CERTARA

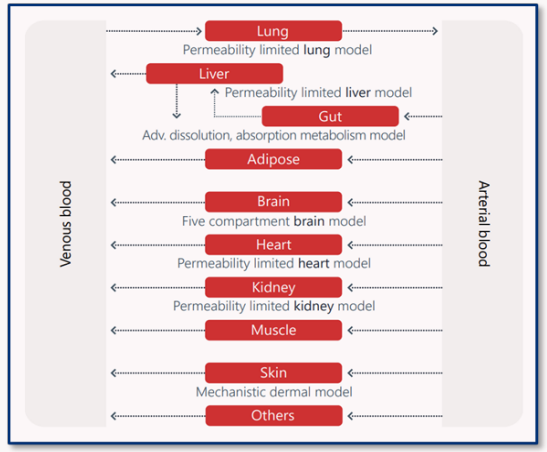
Certara MIDD Platform

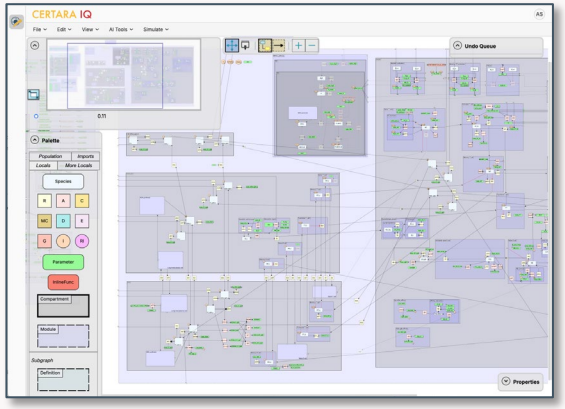
Data Integration & Predictive Analytics Delivering Certainty Across Drug Development



CERTARA

Why Use MIDD in Drug Discovery?





- Define lab objectives to achieve in-vivo (human)TPP
- Use of PBPK/QSP to prioritise molecules with the desired PK/PD profiles
  - Early PK/PD & FIH dose predictions
  - DD risk assessment
  - Early formulation screening
- Prediction of exposure used in early tox studies

CERTARA

Final Comments

Applying mechanistic modeling early provides an opportunity to reduce attrition rates post-Discovery

- Multi-parameter candidate selection targeting a human in-vivo Target Product Profile

The measure of success for these models should not be accuracy, but their ability to (i) increase the probability of successfully advancing a drug candidate (ii) filling knowledge gaps in the decision-making process

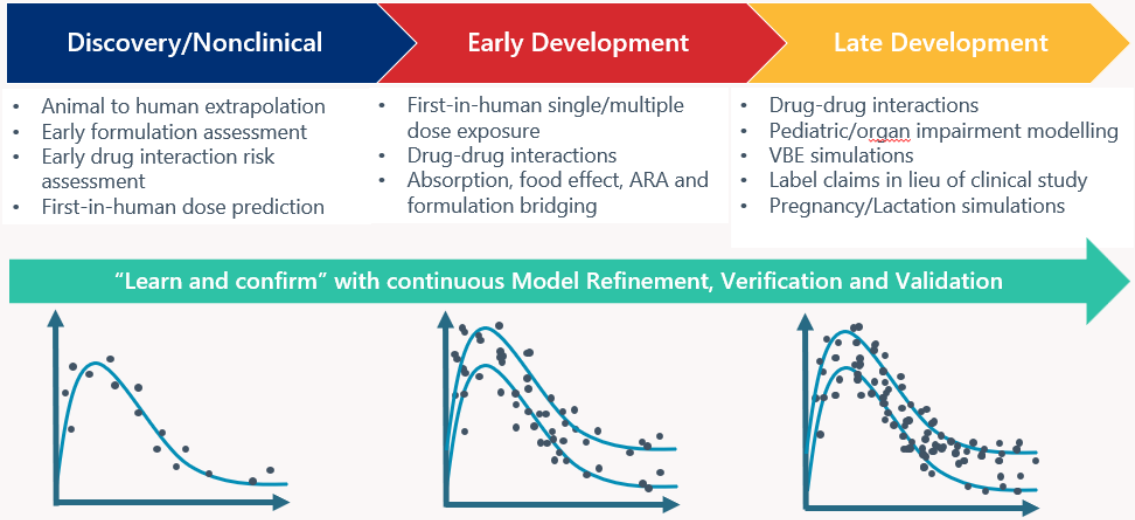
- Something is better than nothing to support decision making

Workflows can improve efficiencies across internal 'silos'

- A shared platform can bring together Modelers, DMPK scientists, Clinical Pharmacologists, Medicinal Chemists and Toxicologists, leveraging MIDD to fill knowledge gaps

Moving into the Clinic, models are …

- Enhanced as more data becomes available, improving their predictive accuracy and reliability
- Accurate enough to answer "what if" scenarios at each stage in the lifecycle of the drug
- Validated to enable extrapolation across populations
- Robust enough to generate data in support of regulatory submissions and label claims
- Re-usable on further support of the drug post-approval



Thank You