QSP - A must have for me !

Current state of QSP science and applications as a key Quantitative Medicine approach

Valeriu Damian

Aug 14, 2024

Significant growth and maturity of QSP field

July 2017

Aug 2024

QSP had grown in the last 7 years

- A lot more QSP **applications**
- Applications across discovery and development
- Many **QSP CROs**
- From lone modelers to dedicated QSP groups
- Many **published QSP** models
- Many QSP models for available for licensing
- Defined **QSP workflows**
- Cross pharma working groups and workshops
- Significant **regulatory interest**
- **Quantitative Medicine** toolbox
- QSP training curricula

Agenda for today

- Must have for me !
- Quantitative Medicine toolbox
- Impact examples
- QSP Workflows
- **Digital Twin**
- **Target Pharmacology Assessment**
- Challenges and opportunities
- Acknowledgements

Must have for me !

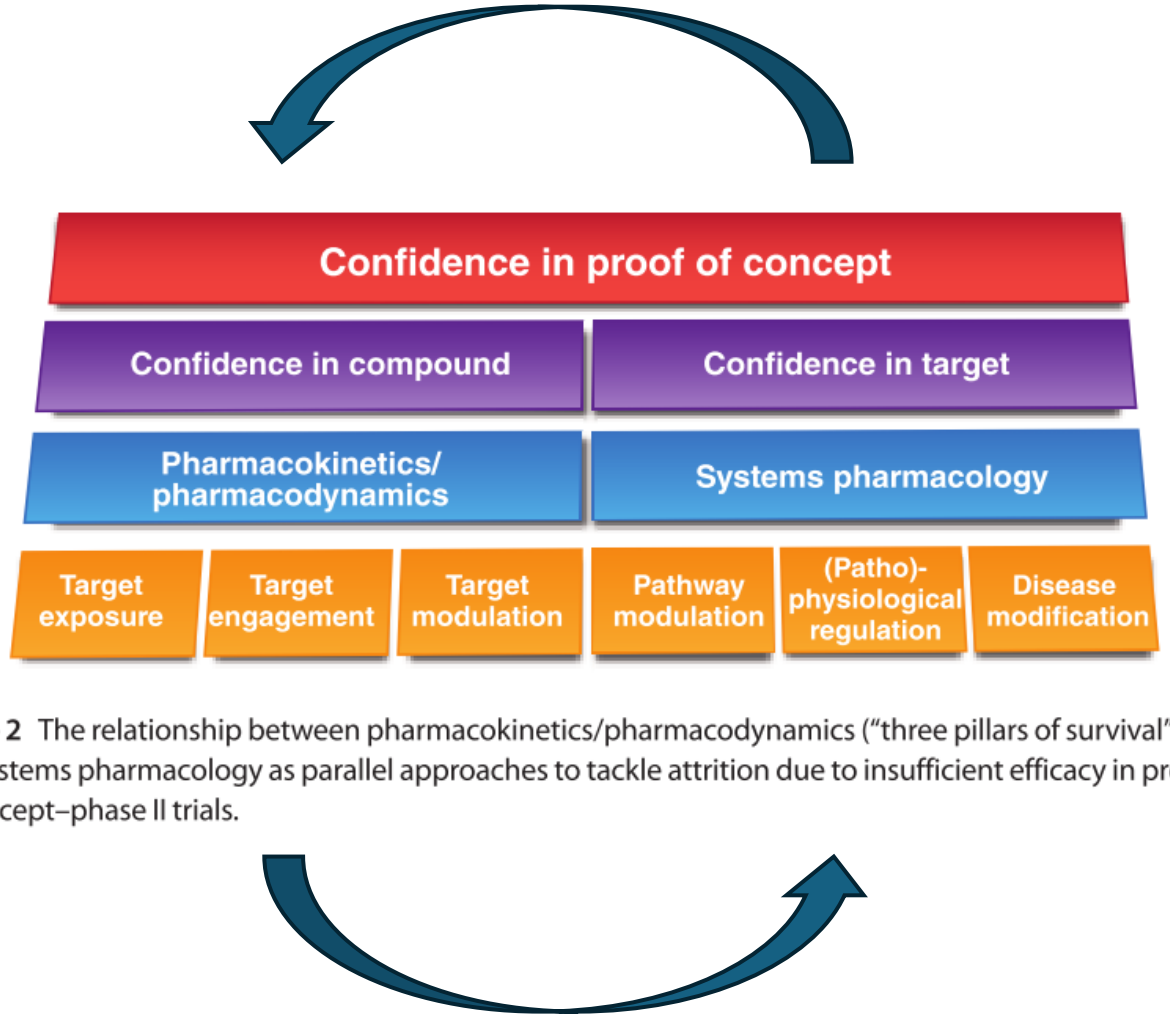
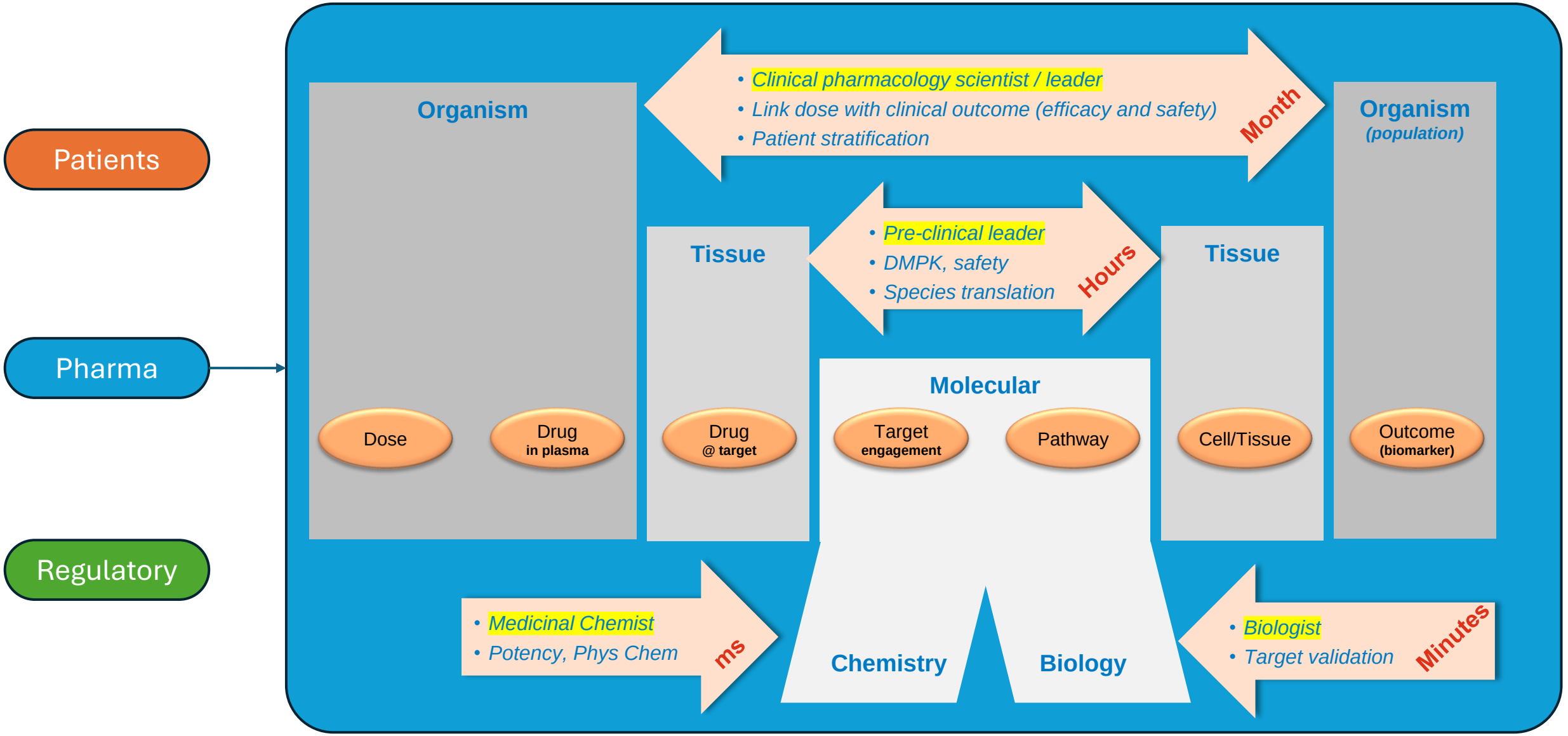


Figure 2 The relationship between pharmacokinetics/pharmacodynamics ("three pillars of survival"[11]) and systems pharmacology as parallel approaches to tackle attrition due to insufficient efficacy in proof-of-concept–phase II trials.

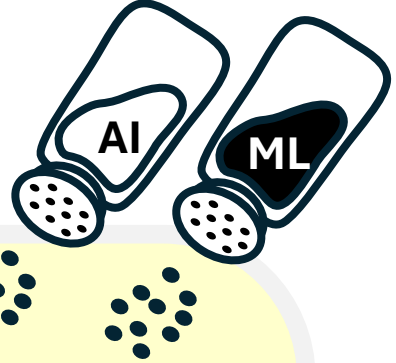
- Gain confidence in the target BEFORE we gain confidence in compound !!!
- To try a novel target in humans takes:
  - 5-7 years
  - Hundreds of millions
- With QSP it is:
  - About 10 times faster !
  - About 100 times cheaper !

Vicini, P. and van der Graaf, P. H. (2013), Systems Pharmacology for Drug Discovery and Development: Paradigm Shift or Flash in the Pan?. Clinical Pharmacology & Therapeutics, 93: 379–381. doi:10.1038/clpt.2013.40

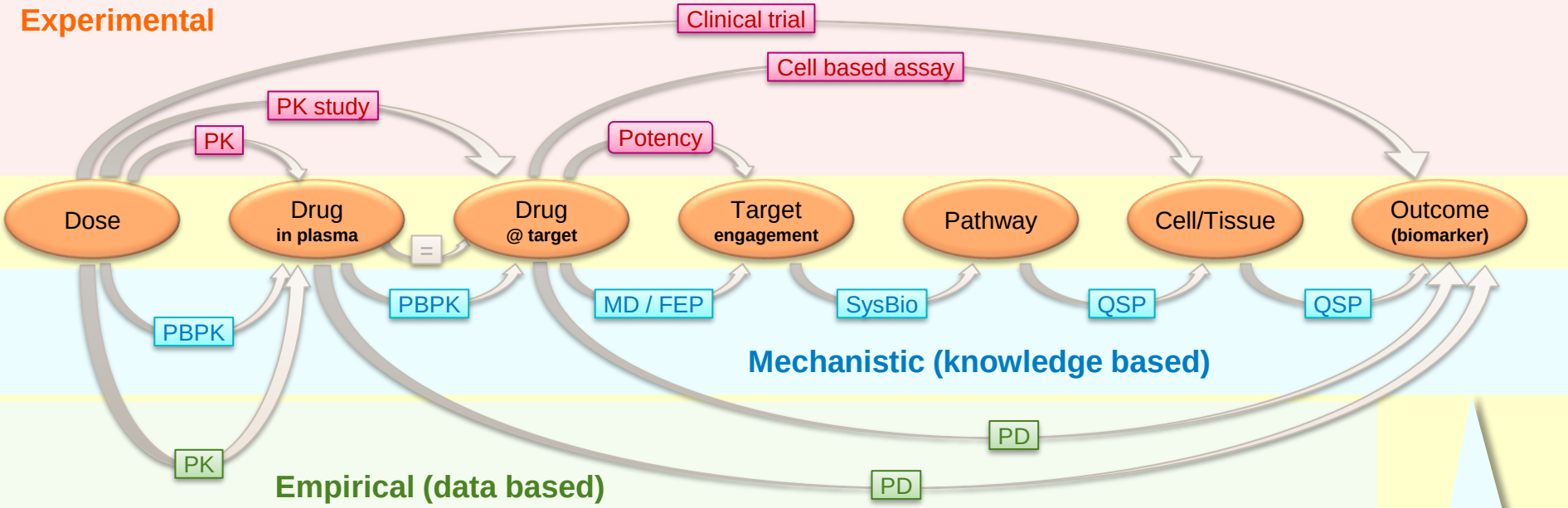
Must have for **ME** … who is “ME” ?



Quantitative Medicine toolbox



- *Costly to generate*
- *Expected if no understanding*
- *Definitive answer… almost all the time*



Artificial Intelligence and Machine Learning

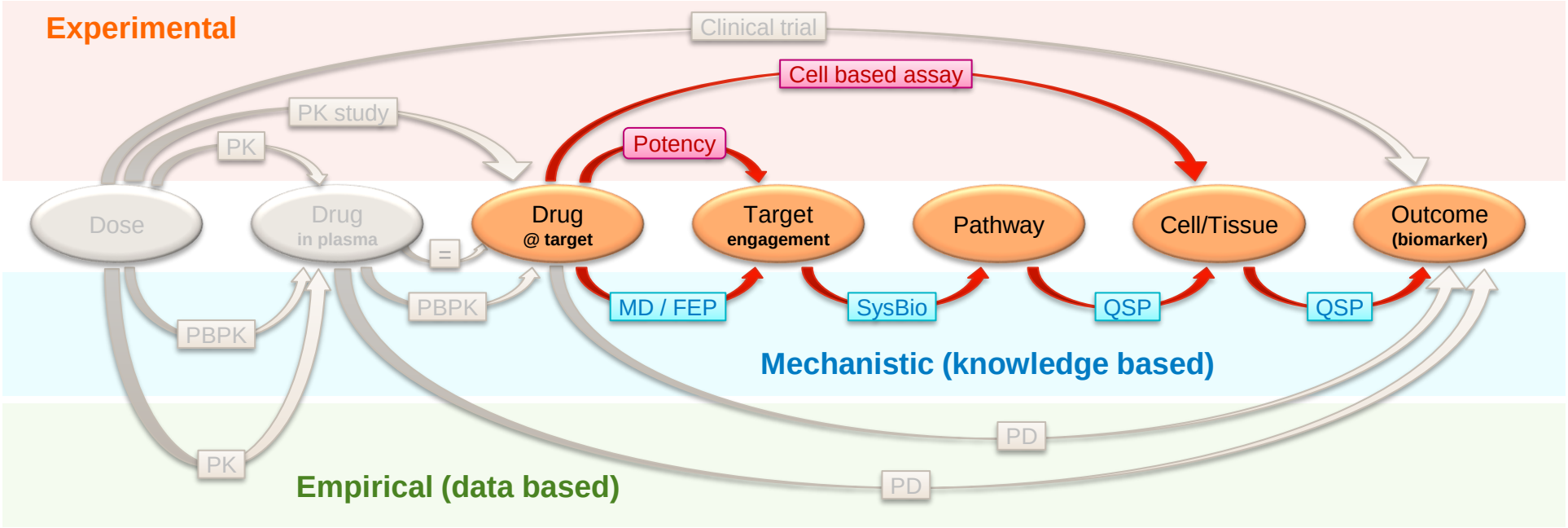
- *Easier to build the model*
- *Easier to defend*
- *Requires costly data*
- *Limited extrapolation*

- *Challenging to build*
- *Challenging to defend*
- *Mostly in-vitro data needed*
- *Understanding and extrapolation*

- *Can improve workflows and it is easy to use* *(just ask ChatGPT ☺)*
- *Can "hallucinate" i.e. give wrong but plausible answers but it improves quicly*

QSP during discovery

Start to build confidence in target using QSP

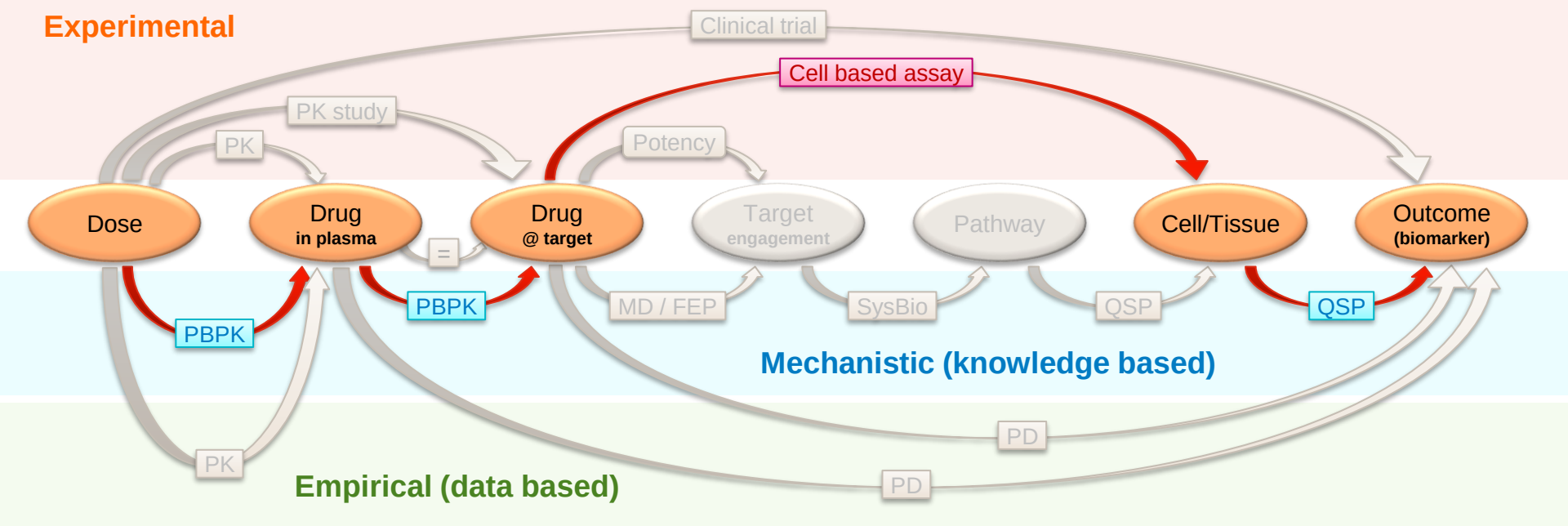


Questions that can be addressed by QSP

- Maximum achievable efficacy vs SoC
- Target engagement needed for efficacy
- Duration of target engagement needed for efficacy
- Optimal balance between potency and ADME
- Early dose estimate
- Evaluate combinations (e.g. bispecifics)
- Best modality to engage the target
- Identify key biology gaps

QSP during translational phase

Leverage PBPK and in-vitro data to predict clinical outcomes and biomarkers

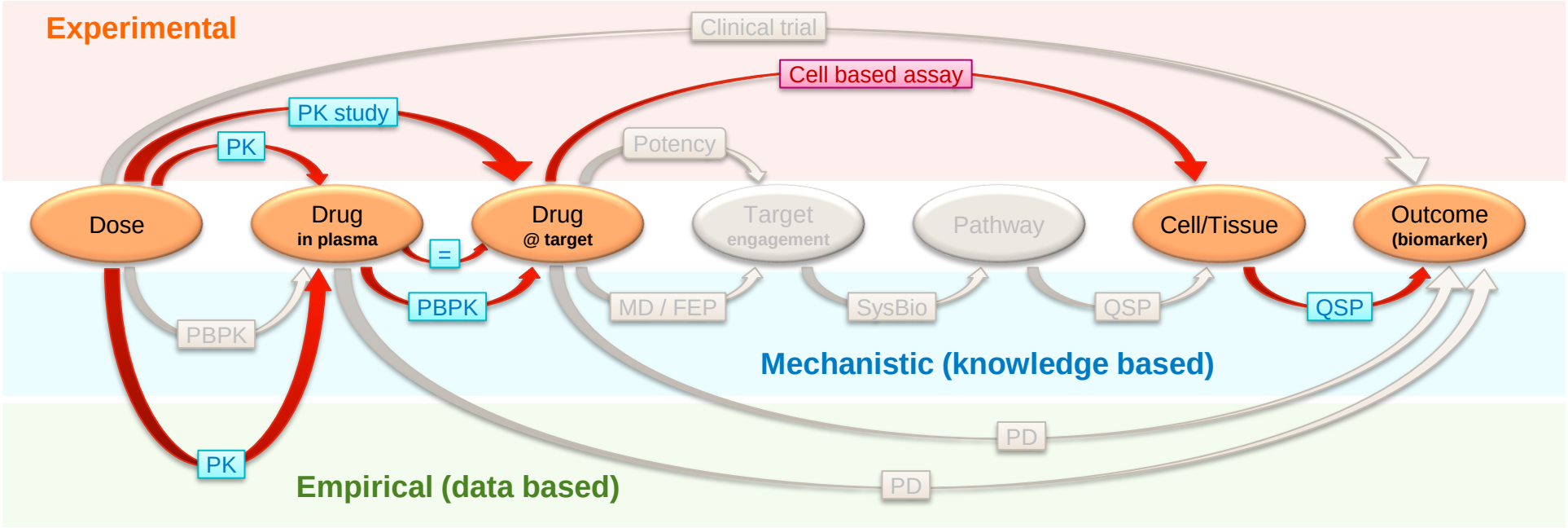


Questions that can be addressed by QSP

- More accurate dose estimates
- Balance efficacy and safety
- Evaluate dosing regimens
- Combination vs sequential treatments
- Evaluate translational biomarkers
- Differentiate response & PK in healthy and patients
- Explore PD effect on PK
- Regulatory engagement

QSP clinical development after FTIH

Use measured PK (popPK) and in-vitro data to predict clinical outcomes and biomarkers



Questions that can be addressed by QSP

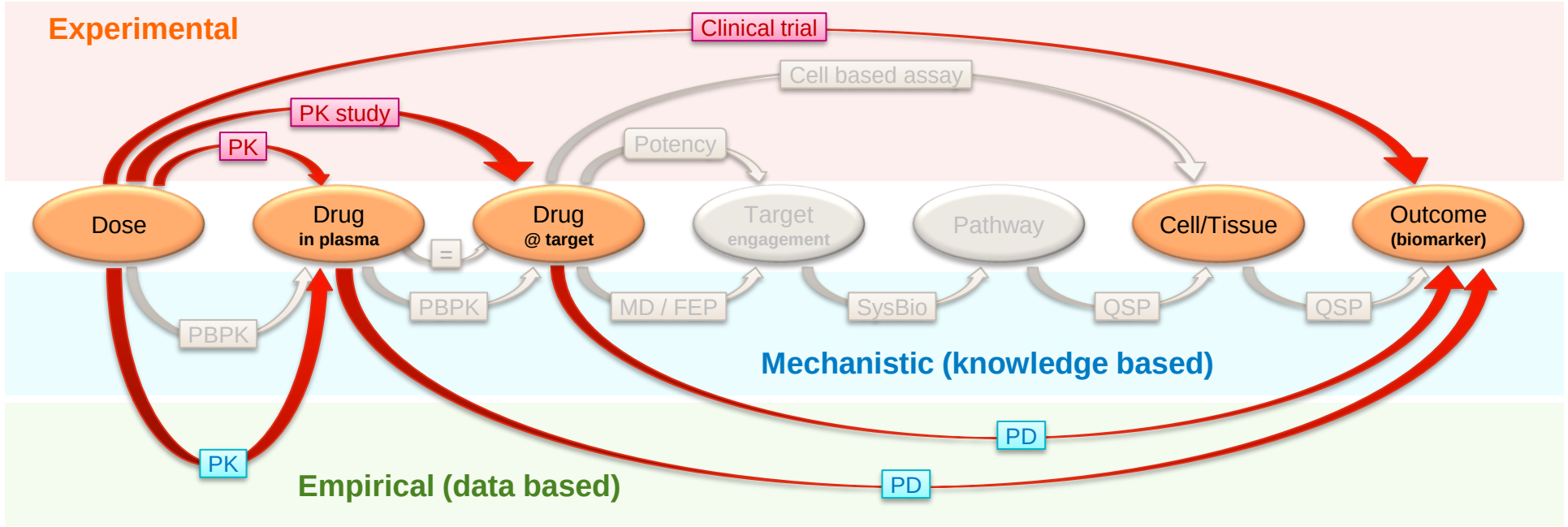
- More accurate dose predictions
- Predicting exposure response
- Help clinical trial design
- Evaluate different patient populations (1L, 2L)
- Estimate patient response variability
- Incorporate Placebo response
- Regulatory engagement

QSP late stage clinical development

Use measured PK and outcomes –(PMX & popPK/PD)

When the answer to the question is
- within the available clinical datasets → use PMX
- spread across multiple data types → use QSP

- Piet van der Graaf

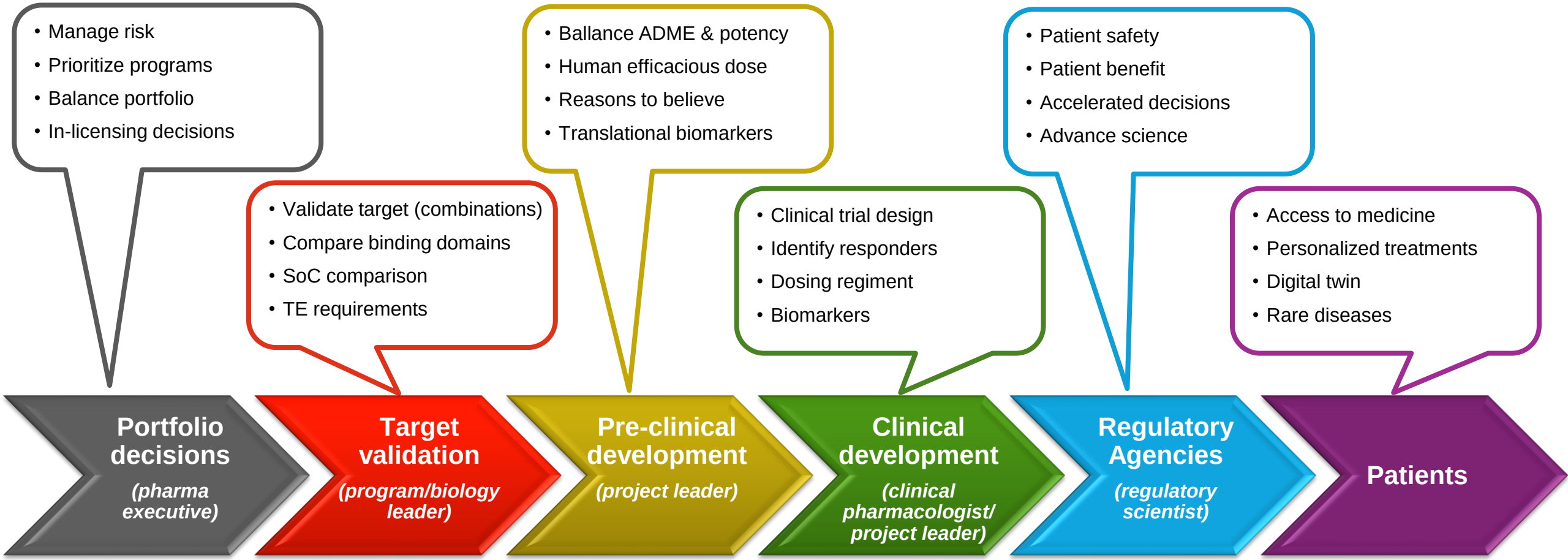


Use QSP for extrapolation if needed

- Leverage available Phase 2 data
- Use Pharmacometrics approaches
- Use QSP for extrapolations if needed (e.g. pediatrics)

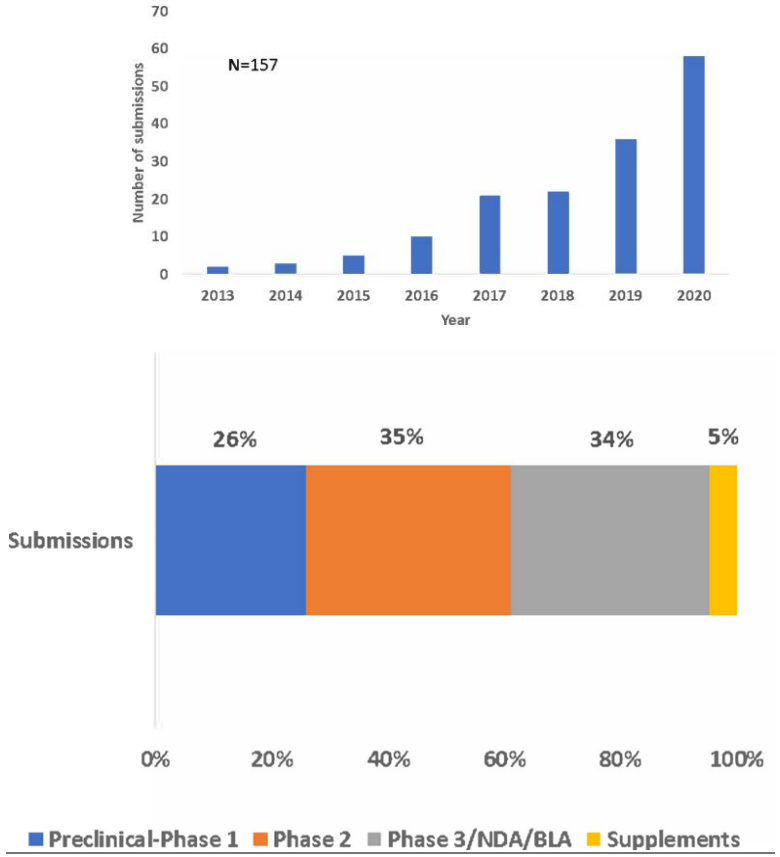
- Leverage PBPK for:
  - DDI
  - Special populations
  - Pediatrics
  - Setting manufacturing specifications

QSP Applications for “ME”

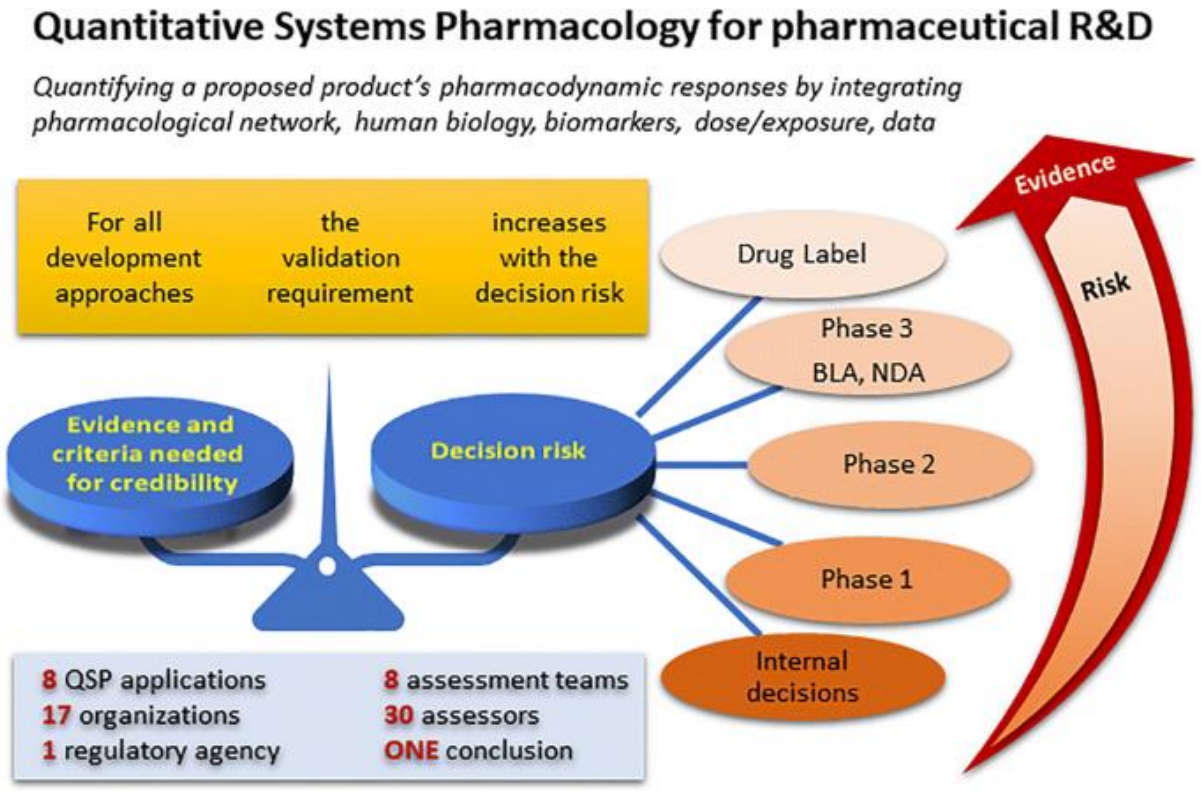


Building trust with regulatory agencies

Quantitative systems pharmacology: Landscape analysis of regulatory submissions to the US Food and Drug Administration



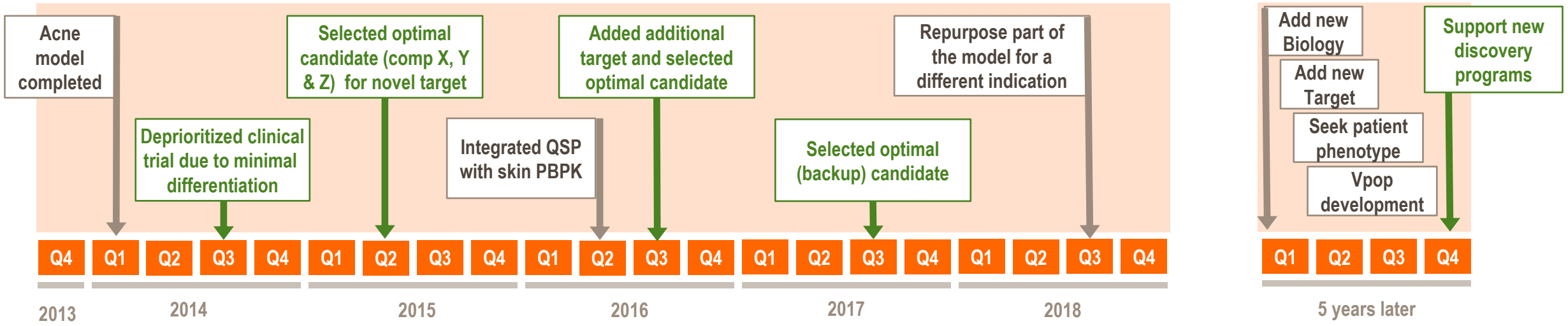
CPT Pharmacom & Syst Pharma, Volume: 10, Issue: 12, Pages: 1479-1484, First published: 03 November 2021, DOI: (10.1002/psp4.12709)

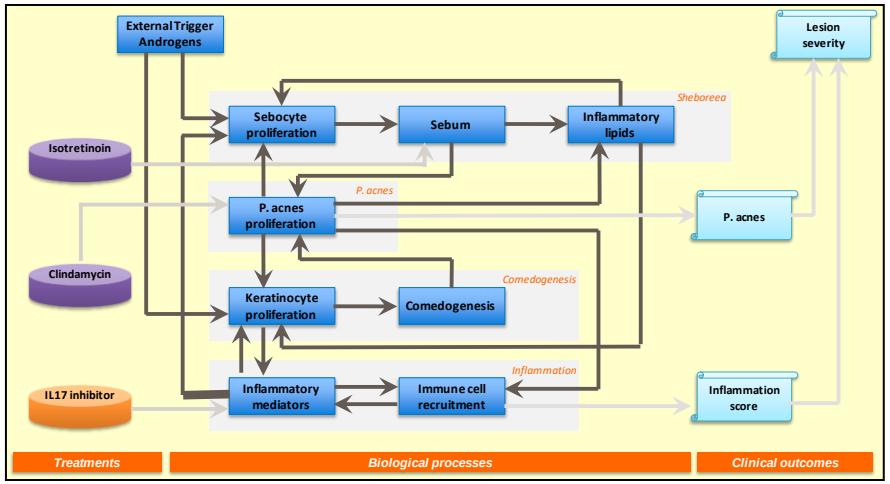


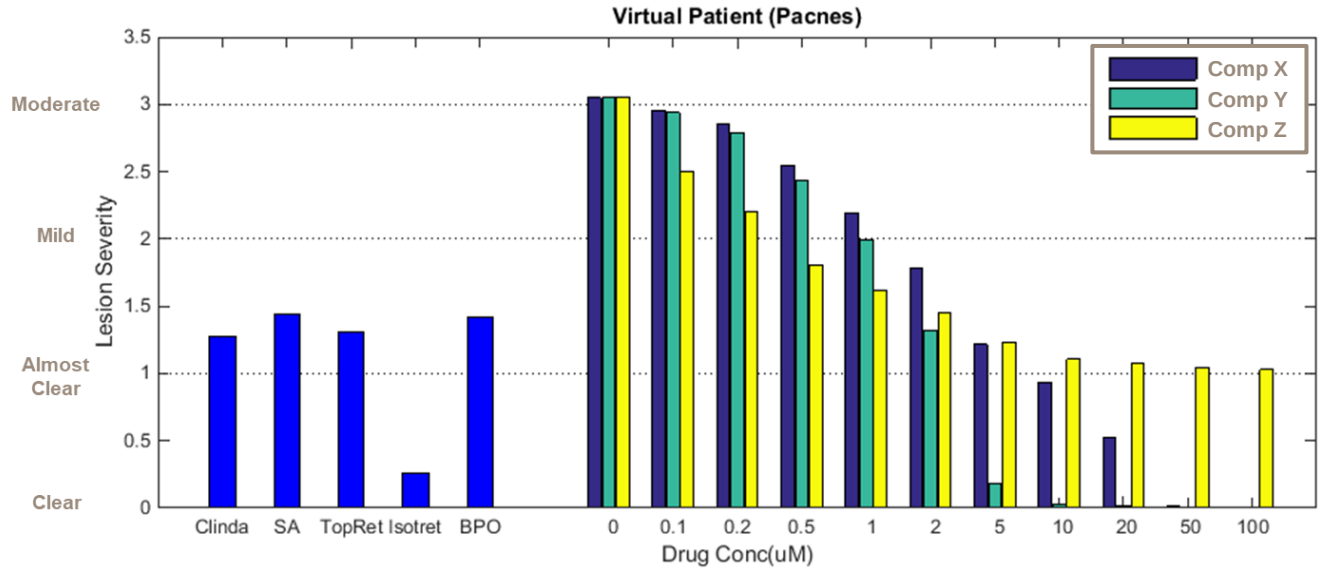
Bai, J.P.F., Schmidt, B.J., Gadkar, K.G. *et al.* FDA-Industry Scientific Exchange on assessing quantitative systems pharmacology models in clinical drug development: a meeting report, summary of challenges/gaps, and future perspective. *AAPS J* **23**, 60 (2021). https://doi.org/10.1208/s12248-021-00585-x

The life of the ACNE platform QSP model

Loveleena Bansal and Cibele Falkenberg

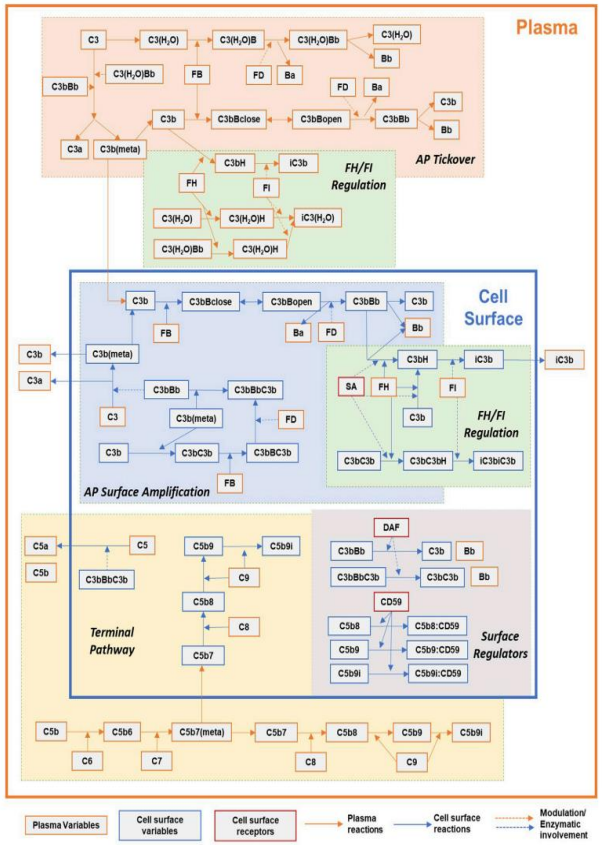


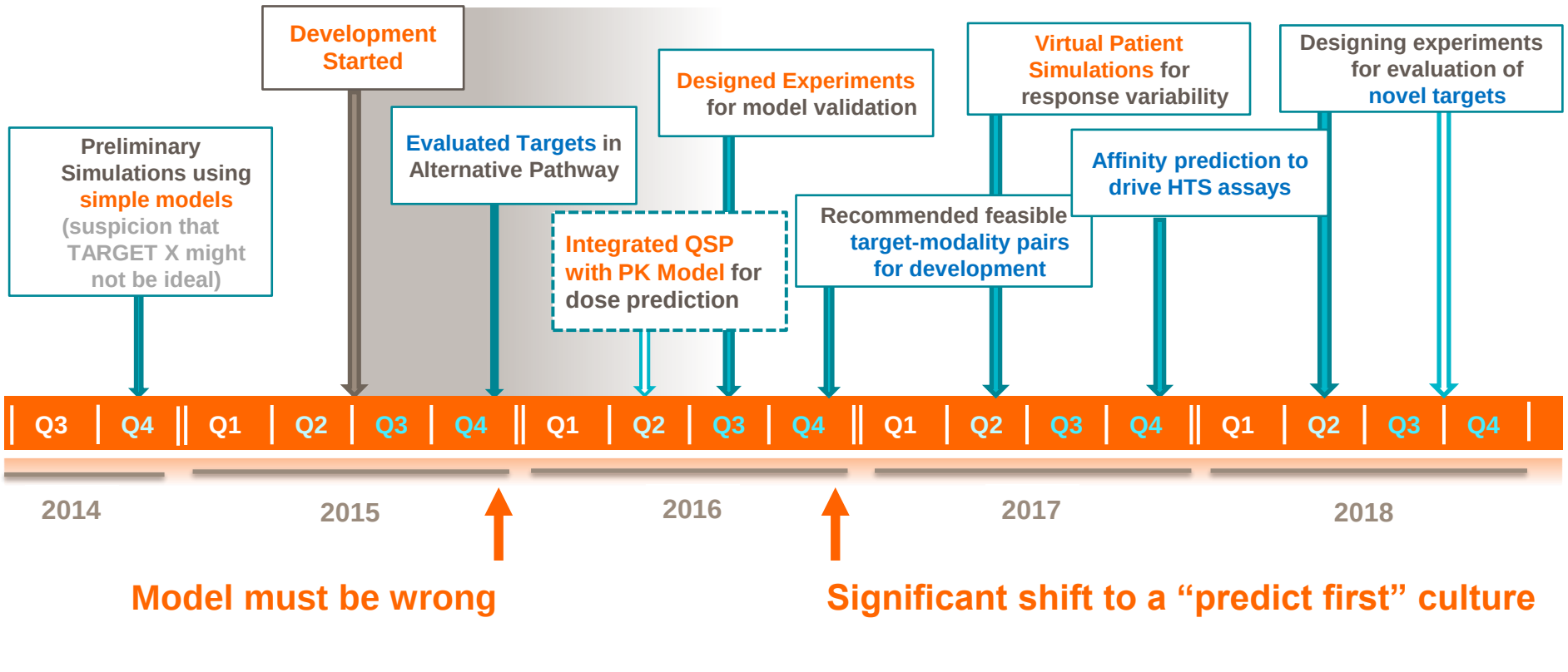




Complement Pathway model – building trust and impact discovery

Loveleena Bansal





	C3	FB	FD	C5	C6	C7	FP	C3b	C3bB open	C3bB close	C3bBb	C3bBb -C3b
A) Small molecule		✓	✓	O								
B) Large Molecule-Ab			x	★	O		O					

Feasible	>90% target inhibition for SM dose <= 100 mg, LM-Ab dose <=20 mg/kg
Challenging	50-90% target inhibition for entire dosing interval or >90% inhibition for at least half of the dosing interval at maximum feasible dose
Infeasible	<50% target inhibition in the desired dose range

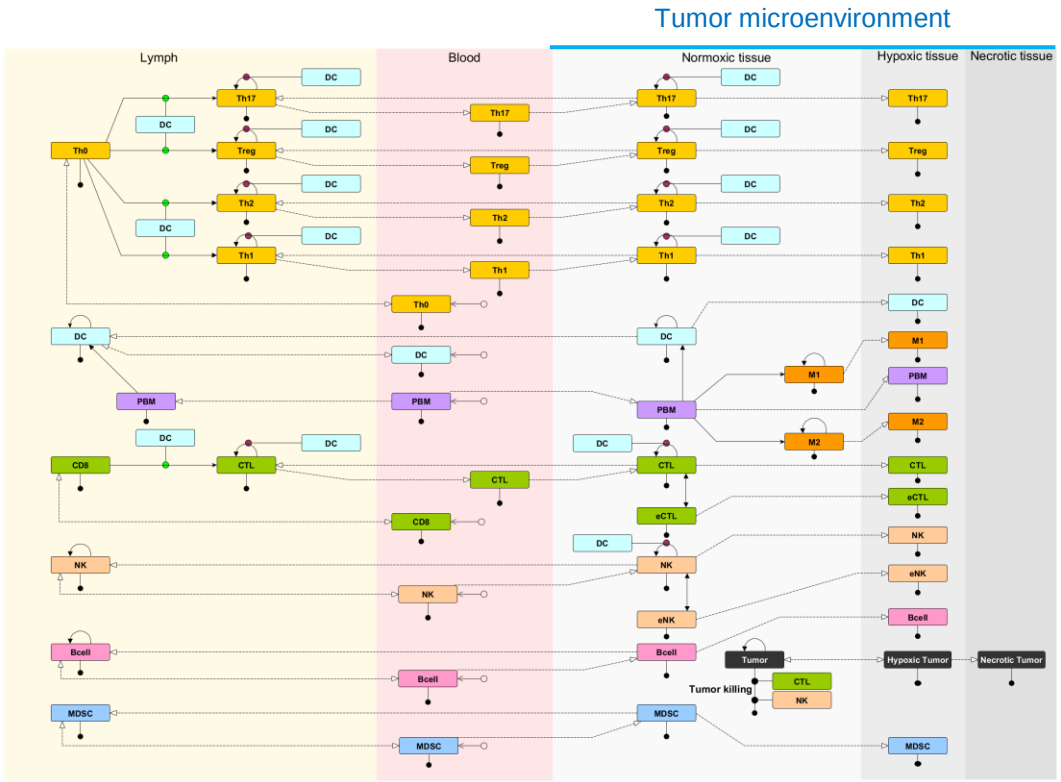
★	Approved drug
✓	In clinical development – positive data
O	In clinical/ preclinical development
x	Terminated

Bansal L, Nichols EM, Howsmon DP, Neisen J, Bessant CM, Cunningham F, Petit-Frere S, Ludbrook S, Damian V. Mathematical Modeling of Complement Pathway Dynamics for Target Validation and Selection of Drug Modalities for Complement Therapies. Front Pharmacol. 2022 Apr 19;13:855743. doi: 10.3389/fphar.2022.855743. PMID: 35517827; PMCID: PMC9061988.

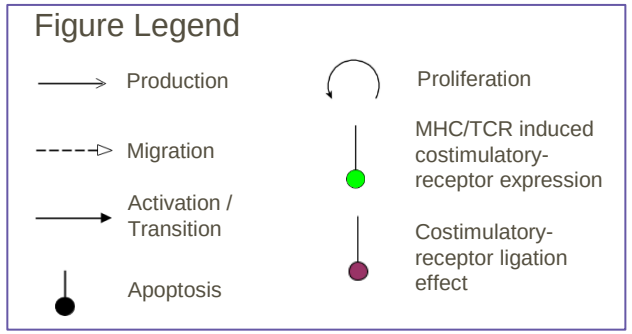
Modular build of IO QSP model - cell-centric overview

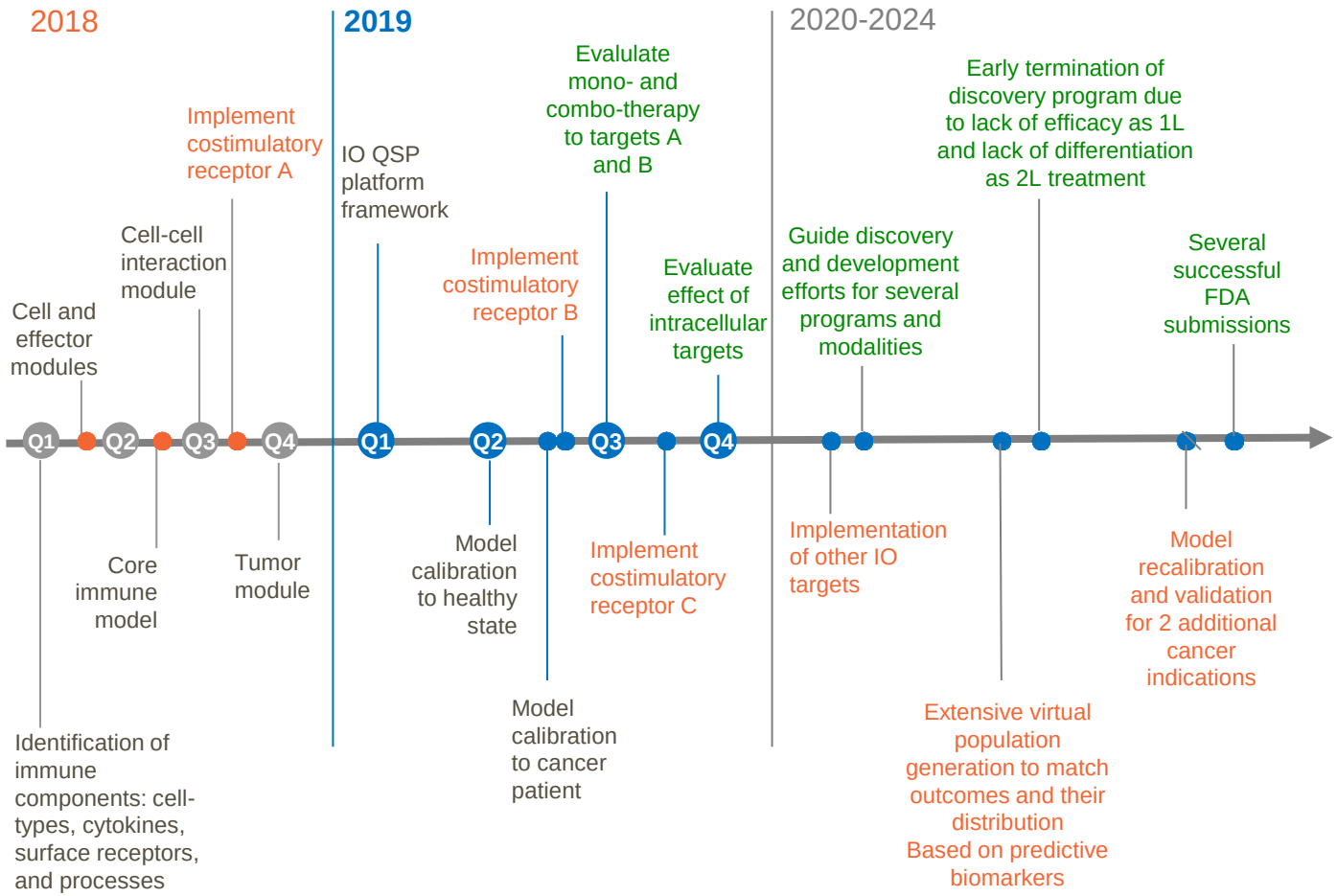
Explicit cell-cell interaction, cytokine and chemokine excluded for simplicity

Roy Song and Aalap Verma



Cell types
Tumor cell (prototypical solid)
Dendritic cells
Type 1 & 2 macrophages
MDSC
B cells
Th0/1/2/17/Reg (CD4+) T cells
Naïve CD8+ / mature CTL T cells
NK cells





Program questions addressed by QSP & TPA in one year

Discovery

- Level of target engagement required for efficacy. 10
- Best modality / mode of action for a target. 1
- Combination evaluation. 2
- Maximum achievable efficacy vs SoC 4
- Optimal potency/ADME balance for efficacy 7
- Identify key biology gaps 1
- Leverage for automated design 2

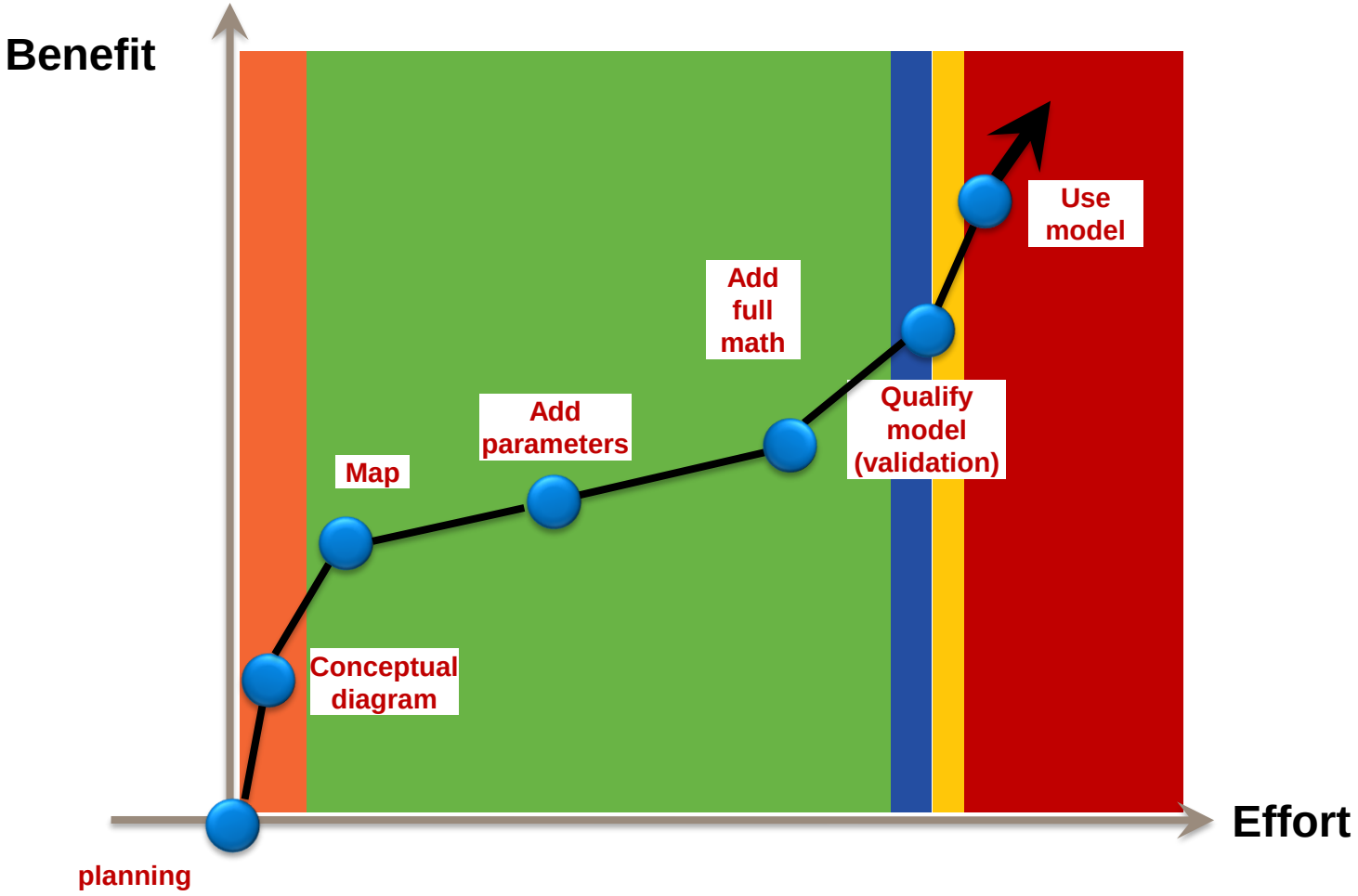
QSP & TPA

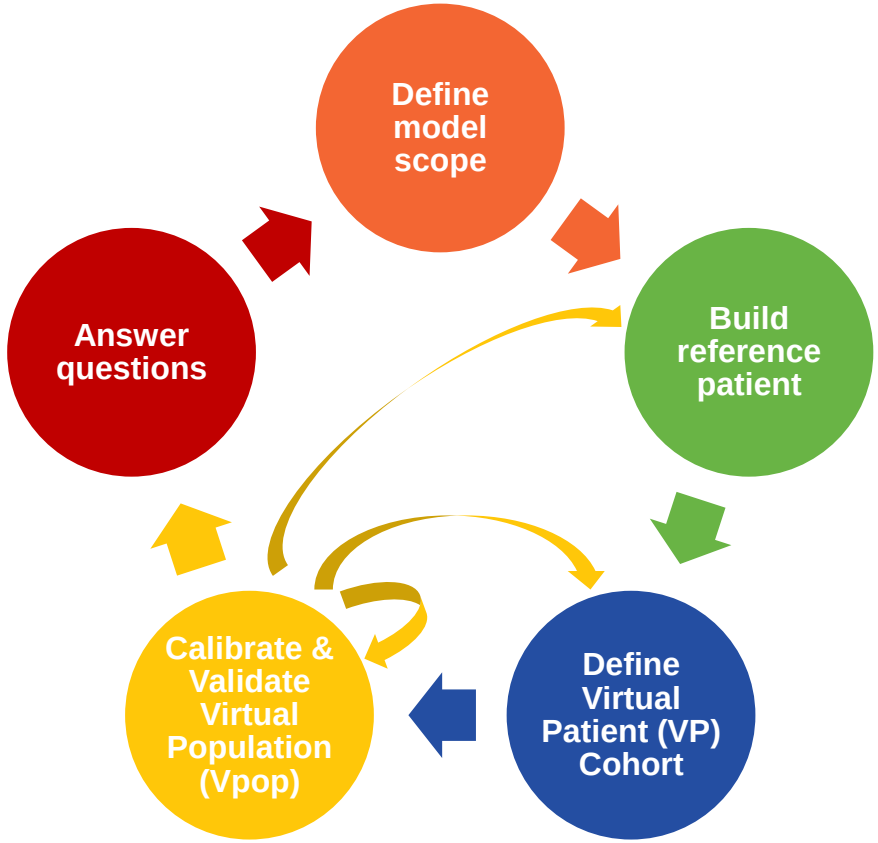
Numbers represent the questions addressed using QSP in 2022

Clinical and translational

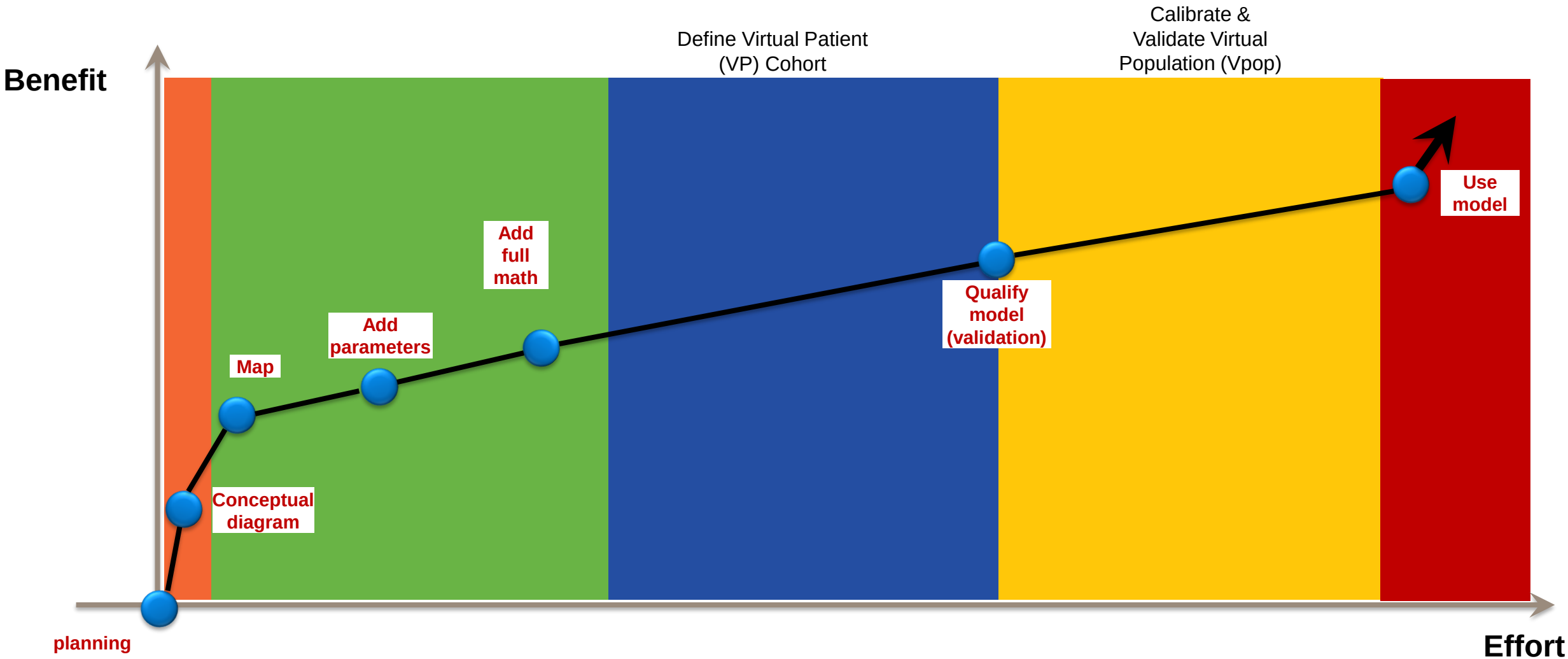
- 4 Combination evaluation
- 5 Comparison with SoC/ Competitor
- 4 Dose and regimen optimization
- 3 Patient stratification and responder analysis
- 1 Biomarker evaluation
- 1 Trial design
- 1 Treatment positioning (1L, 2L)

QSP modeling workflows – comparison with 2017





QSP modeling workflow



QSP workflow – Focus on calibration and validation

Starting point: Clearly defined scope (e.g. disease, questions to address)

Define interventions
e.g. targets, drugs, Std of care

Define outputs
e.g. biomarkers, outcomes

Gather available data
e.g. publications

Separate calibration and validation data

Define model
e.g. processes, reuse models

Calibrate parameters
e.g. based on in-vitro data

Select VP parameters
e.g. sensitivity analysis

Generate VP's

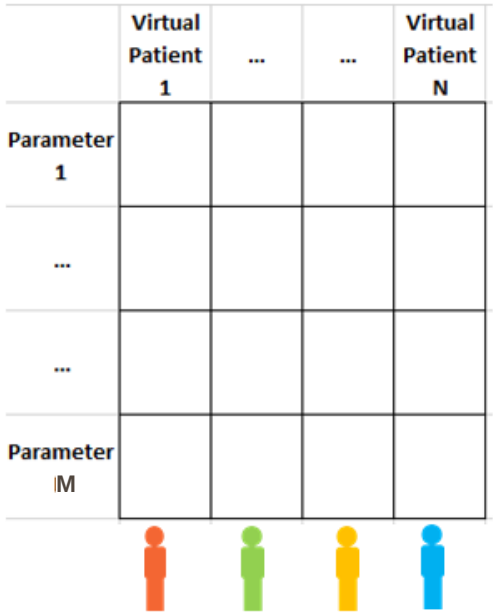
Select plausible VP's

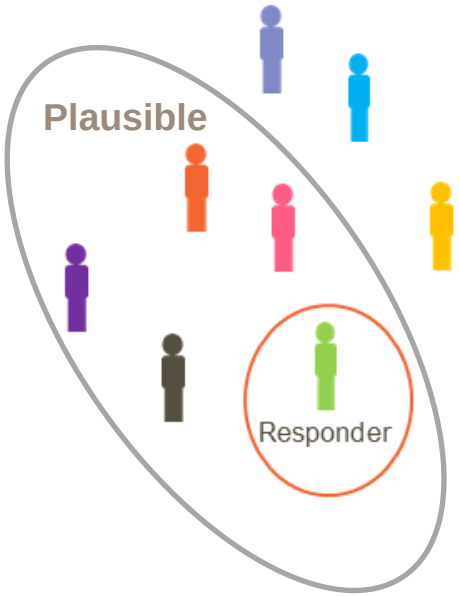
Calculate a Vpop to match all calibration data

Validate Vpop based on validation data

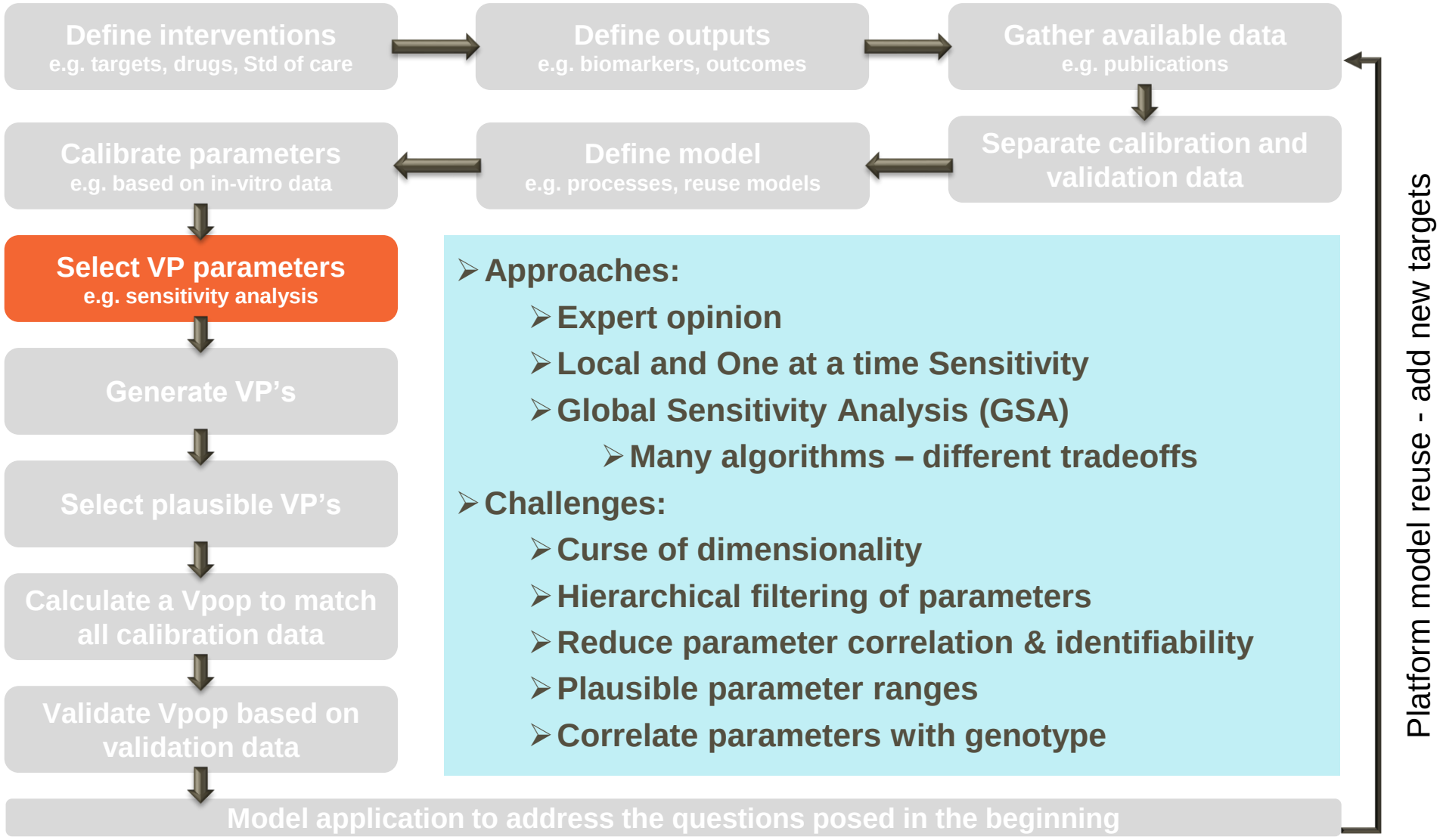
Model application to address the questions posed in the beginning

Platform model reuse - add new targets

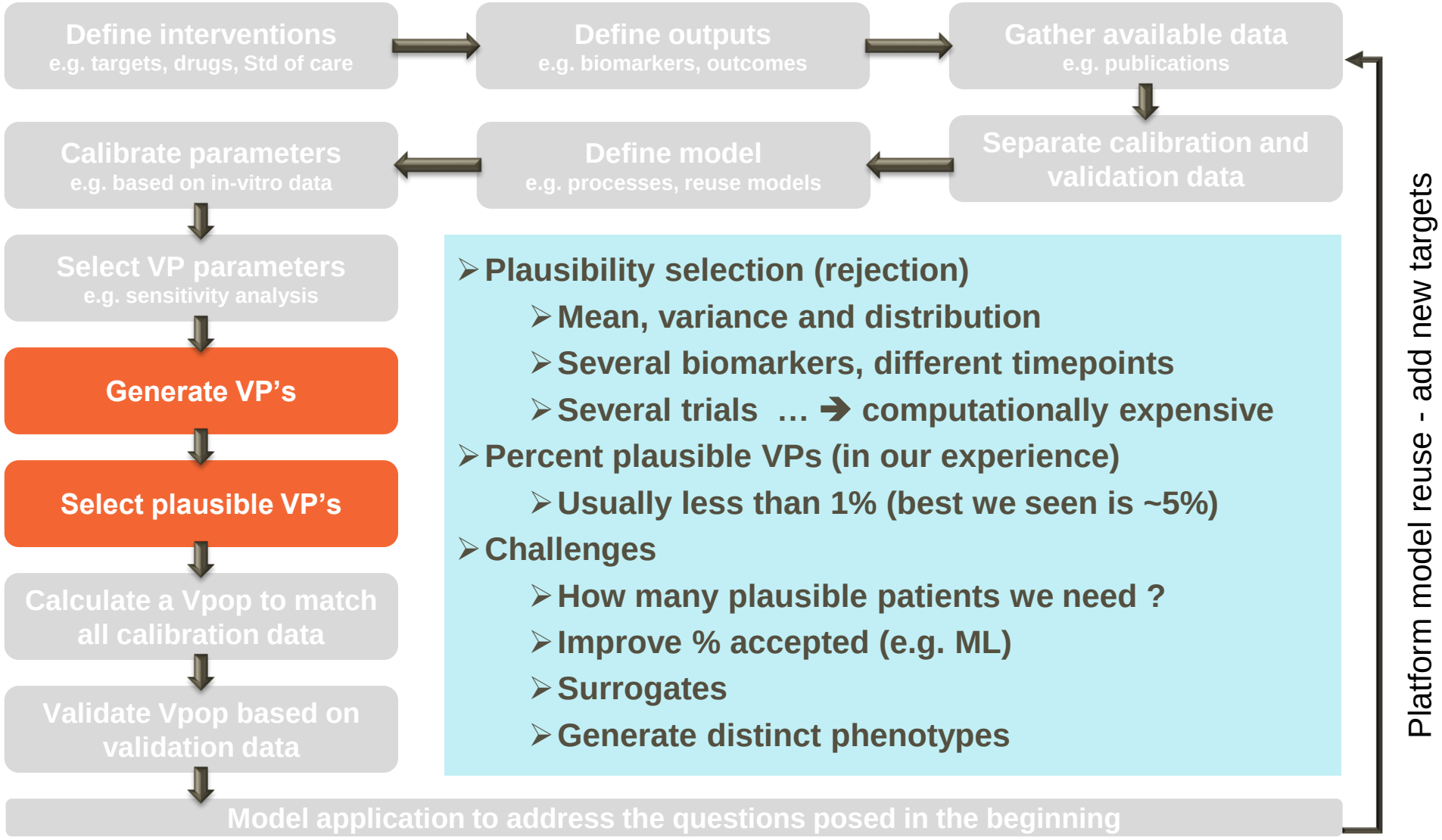




Select Parameters to define virtual patients

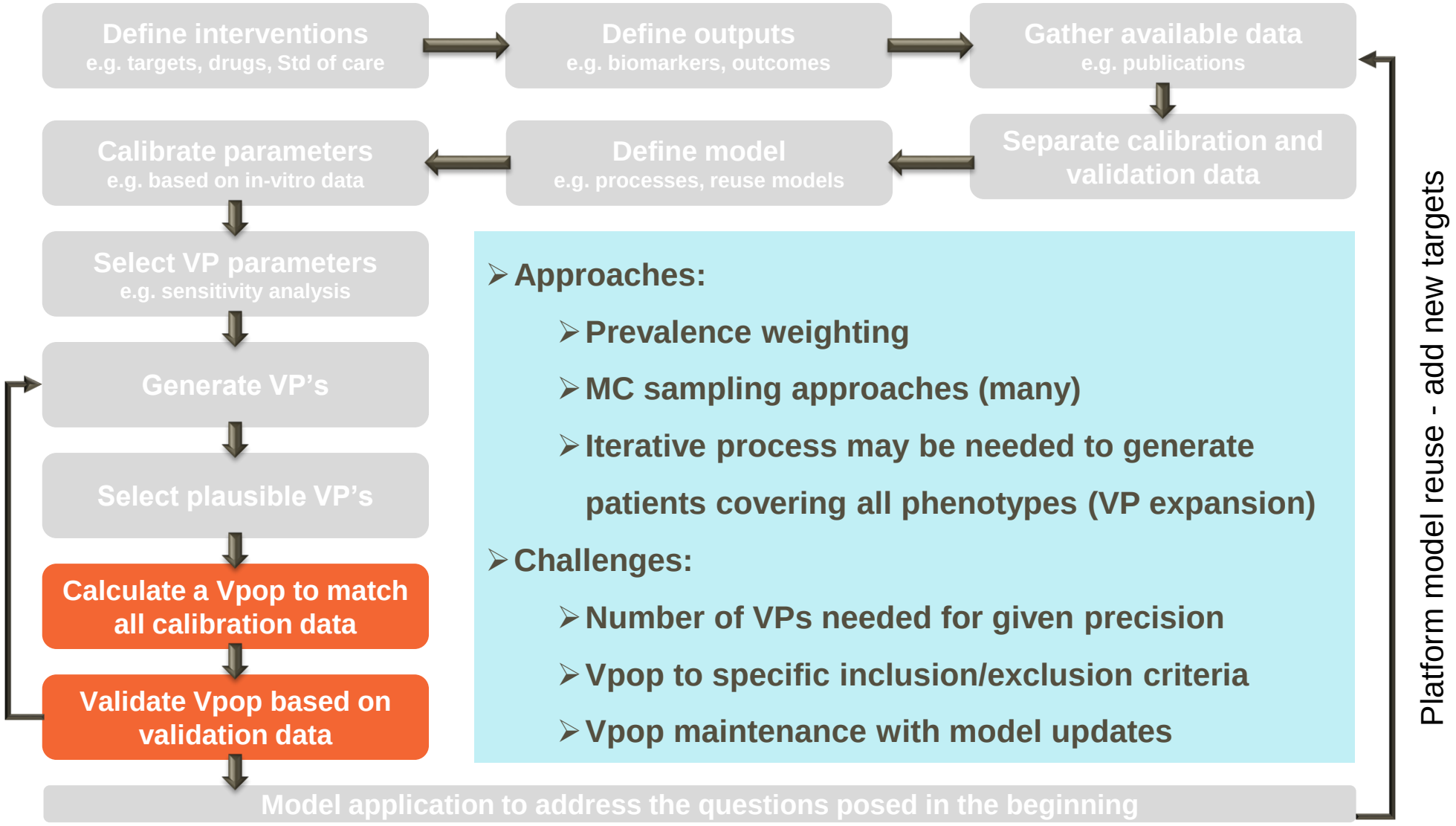


Virtual Patients generation

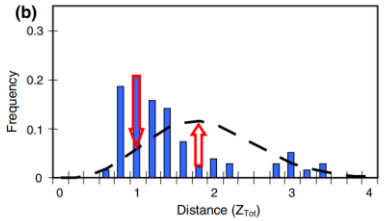


- Plausibility selection (rejection)
  - Mean, variance and distribution
  - Several biomarkers, different timepoints
  - Several trials … ➔ computationally expensive
- Percent plausible VPs (in our experience)
  - Usually less than 1% (best we seen is ~5%)
- Challenges
  - How many plausible patients we need ?
  - Improve % accepted (e.g. ML)
  - Surrogates
  - Generate distinct phenotypes

Generate virtual population to match all calibration data



A few of the Virtual Population papers between 2007-2023

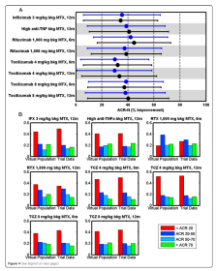


2007

D Klinke
Integrating Epidemiological Data into a Mechanistic Model of Type 2 Diabetes: Validating the Prevalence of Virtual Patients (PMID: 18046647)

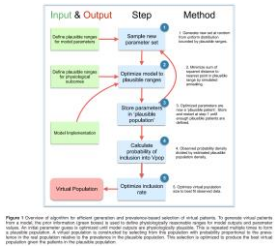
2013

BJ Schmidt, et al
Alternate virtual populations elucidate the type I interferon signature predictive of the response to rituximab in rheumatoid arthritis (PMID: 23841912)



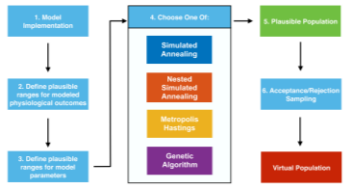
2016

RJ Allen, et al
Efficient Generation and Selection of Virtual Populations in Quantitative Systems Pharmacology Models (PMID: 27069777)



2017

Y Cheng et al.
QSP Toolbox: Computational Implementation of Integrated Workflow Components for Deploying Multi-Scale Mechanistic Models (PMID: 28540623)

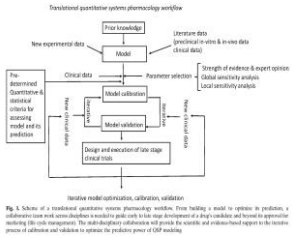


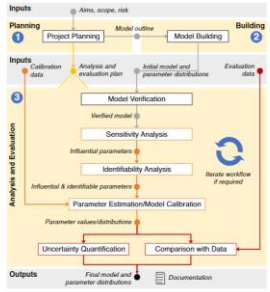
2018

T.R. Rieger et al
Improving the generation and selection of virtual populations in quantitative systems pharmacology models (PMID: 29902482)

2019

J Bai et al (US-FDA)
Translational Quantitative Systems Pharmacology in Drug Development: from Current Landscape to Good Practices (PMID: 31161268).



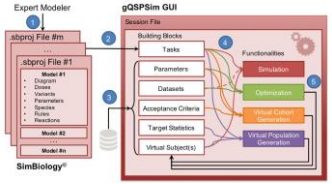


2020

S Braakman, et al
Evaluation framework for systems models (PMID: 34921743)

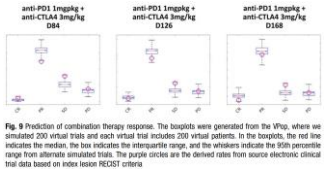
2021

Iraj Hosseini et al,
gQSPSim: A SimBiology-Based GUI for Standardized QSP Model Development and Application (PMID: 31957304)



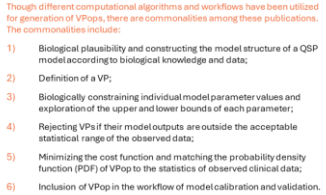
2022

Y Cheng, et al –BOOK chapter
Virtual Populations for Quantitative Systems Pharmacology Models (PMID: 35437722)



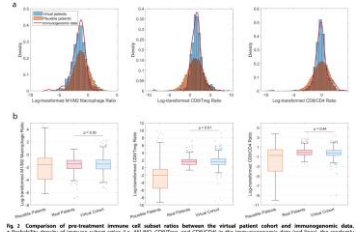
2023

J Bai et al (US-FDA)
Modeling Clinical Phenotype Variability: Consideration of Genomic Variations, Computational Methods, and Quantitative Proteomics (PMID: 36279954)



2023

H Wang et al
Generating immunogenomic data-guided virtual patients using a QSP model to predict response of advanced NSCLC to PD-L1 inhibition (PMID: 37291190)



Digital twin

Digital twin

Definition (from Wikipedia)

- A **digital twin** is a digital model of
  I. an intended or actual real-world **product, system, or process**
  II. that serves as the effectively indistinguishable digital counterpart of it **for practical purposes**

Therefore to define a digital twin one needs to specify:

I. A system or process
II. A purpose

	System	Purpose	Otherwise known as
Digital twin for	Disease X	Predicting disease X population response to therapies	QSP for disease X
	Drug Y	Predicting population exposure for Drug Y	PBPK for drug Y
	Patient Z & Drug Y	Predicting individual exposure for Patient Z to the Drug Y	PBPK for Drug Y parametrized for Patient Z
	Patient Z & Disease X	Predicting individual response to therapy for patient Z	QSP for disease X parametrized to match patient Z response

Note: A Digital twin for Patient Z and Disease X is a Virtual Patient (VP), but not all VPs are Digital twins !

Digital twin definition continued – bone marrow transplant example

Definition (from Wikipedia)

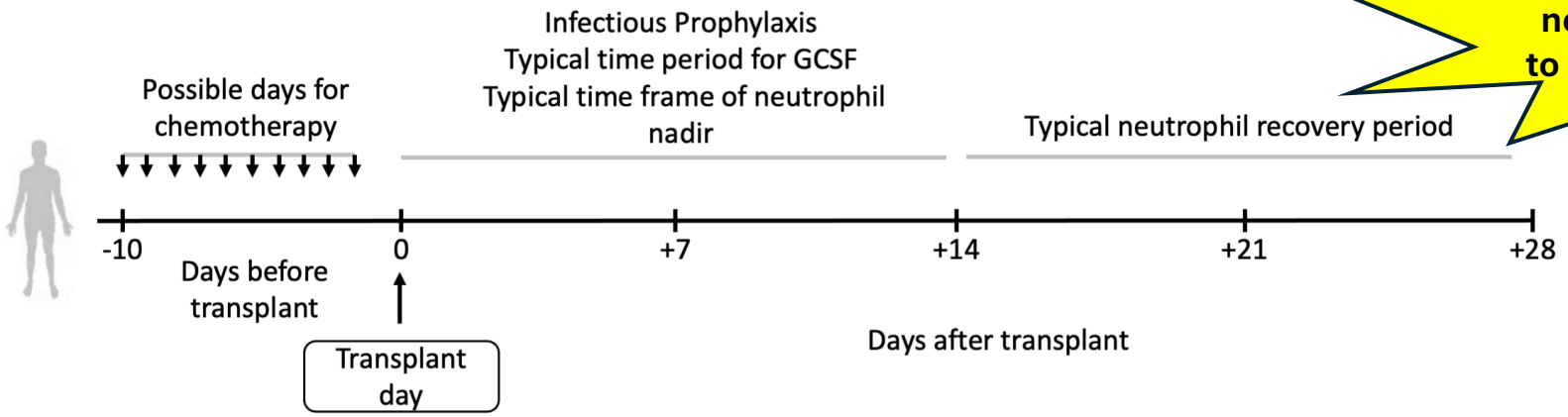
- A **digital twin** is a set of **adaptive models** that emulate the behavior of a physical system in a virtual system getting **real time data to update itself** along its life cycle

Therefore

- A digital twin is the best that can be done based on the available data for the system
- Adapts when new data is available

How much data do we need about patient Z to build a digital twin ?

Typical bone marrow transplant

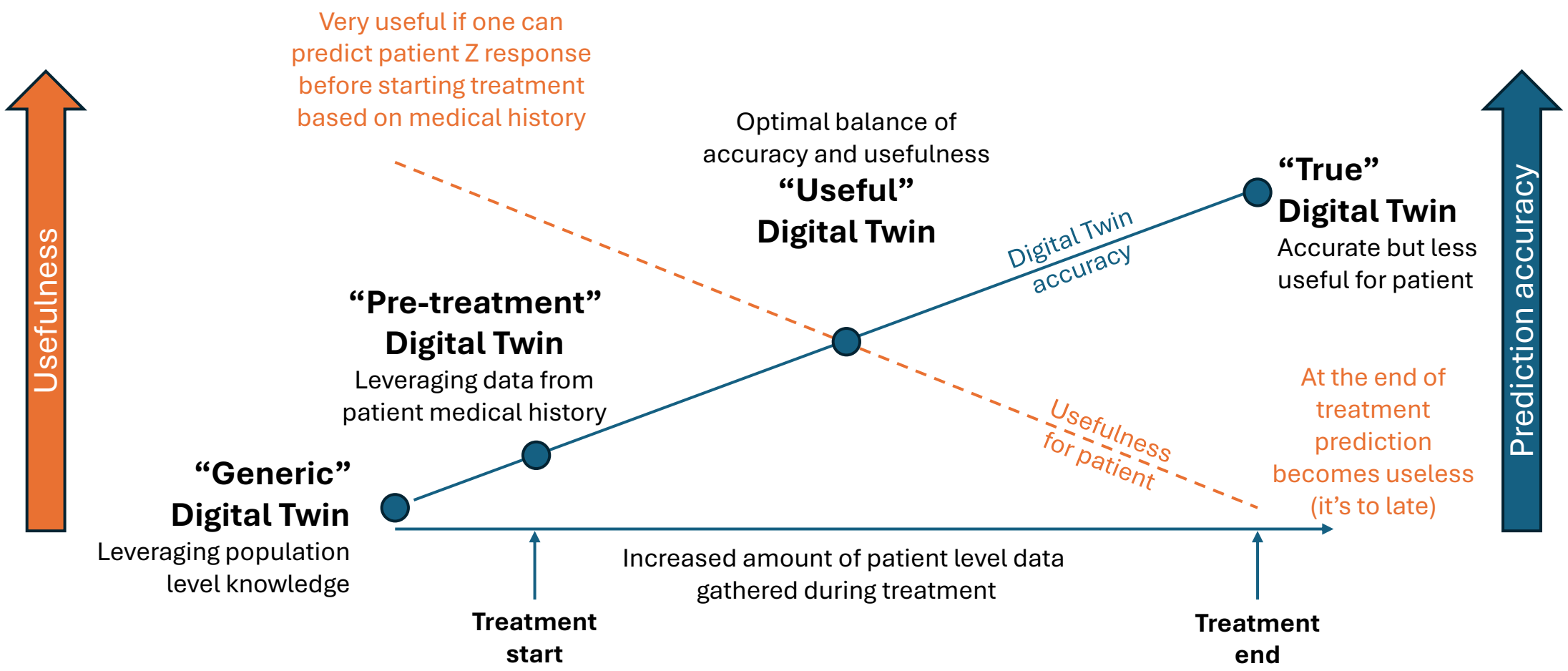


	System	Purpose	Otherwise known as
Digital twin for	Bone marrow transplant	Predicting population neutropenic state	QSP for bone marrow transplant
	Patient Z undergoing bone marrow transplant	Predicting most likely patient Z response to administer optimal rescue treatment	Parametrization of the QSP for bone marrow transplant for patient Z

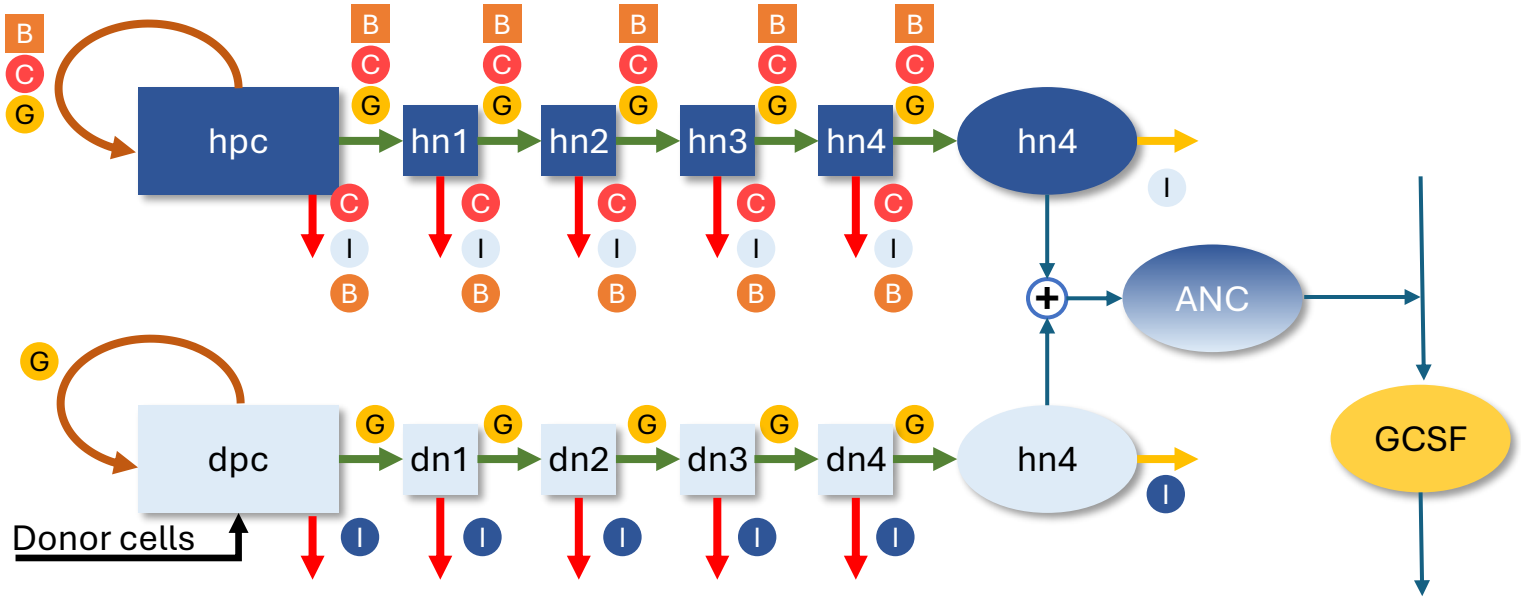
Usefulness and **Accuracy** tradeoff

Digital twin for Patient Z undergoing bone marrow transplant for predicting the optimal rescue treatment

*How much data do we need about patient Z to build a **USEFULL** digital twin ?*



Neutropenia QSP model for bone marrow transplant



Proliferation
Transit/Maturation
Apoptosis in blood
Apoptosis in bone marrow

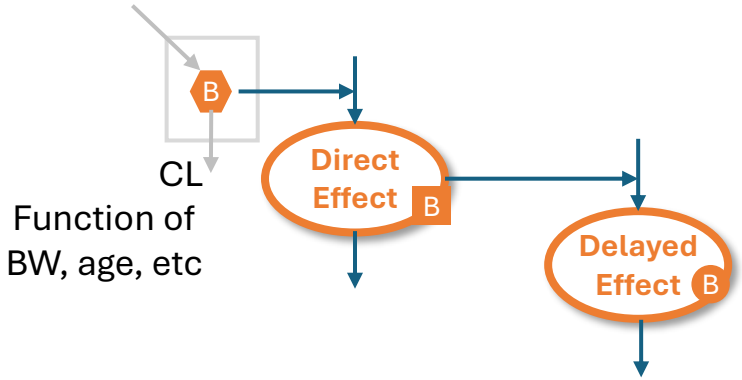
C Chemo (other)
G GCSF effect (based on GCSF receptor)
I Host immune system
I Donor immune system
B Busulfan PK
B Busulfan Direct Effect
B Busulfan Delayed Effect

Cells comprising host immune system

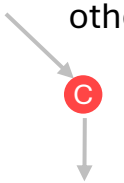
I = hpc+hn1+hn2+hn3+hn4

Cells comprising donor immune system

I = dpc+dn1+dn2+dn3+dn4



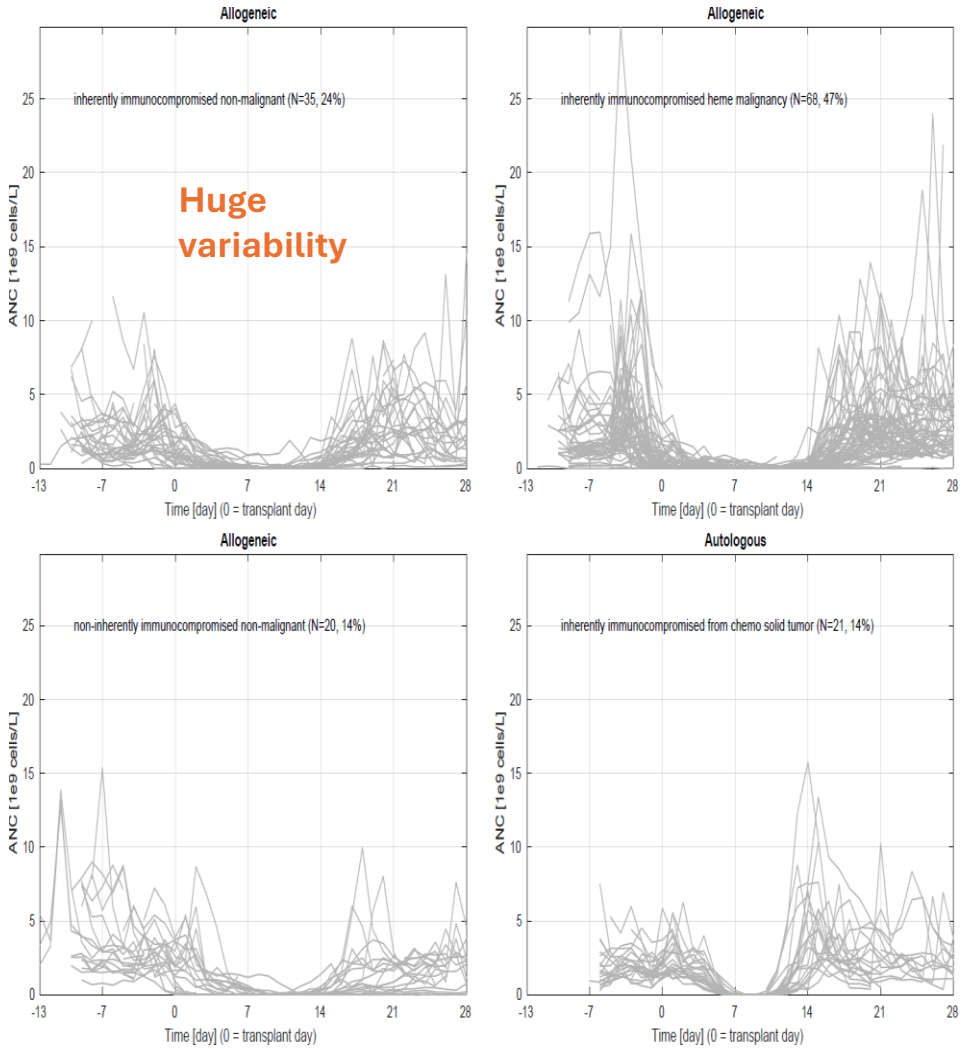
Generic model for other chemo



Model prediction accuracy for various patient groups

Each patient has different age, preexisting conditions, chemo, treatments, donor and rescue medication

Beth Winger
Joseph Polli
Janel Long-Boyle
Andrew Weber
Jordan Brooks
Jaimit Parikh

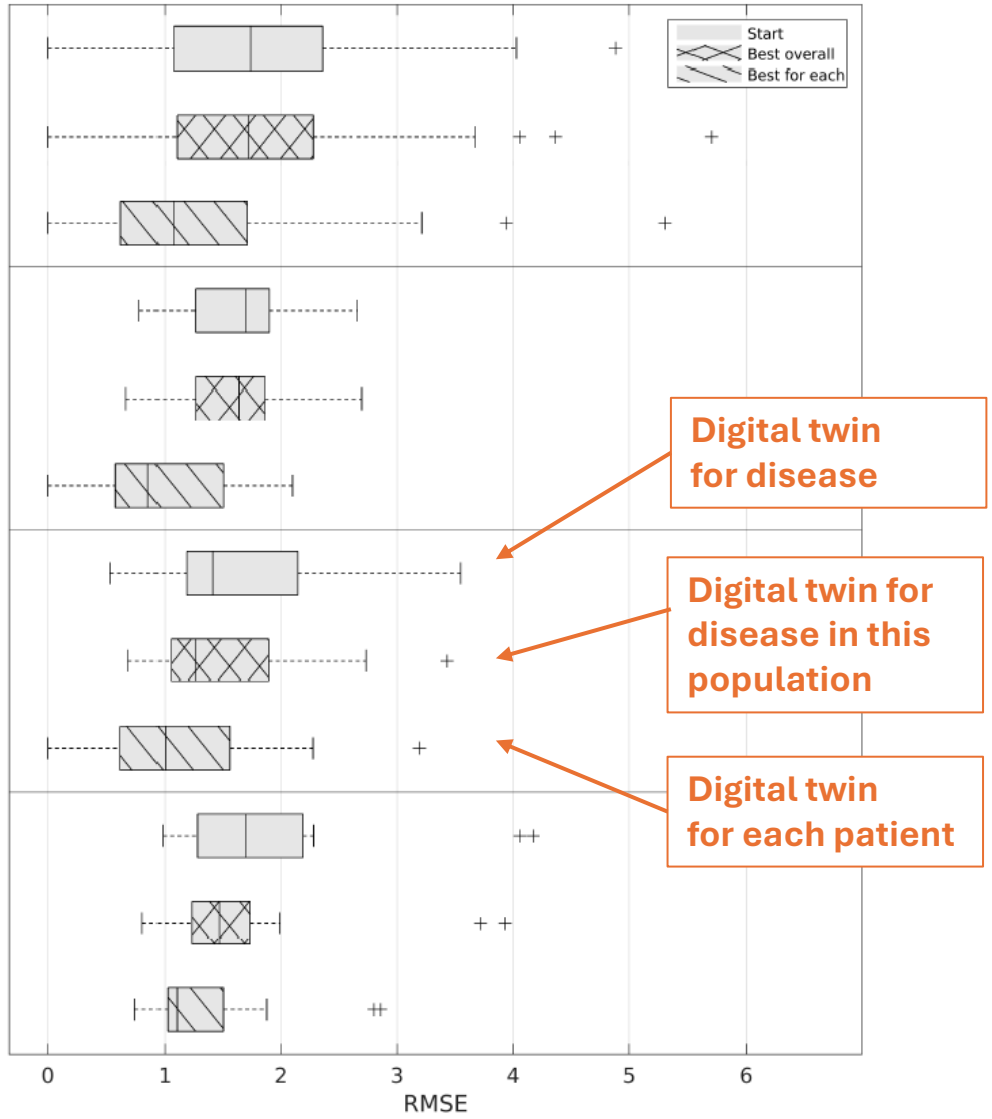


Allogeneic
inherently immunocompromised
heme malignancy

Allogeneic
non-inherently immunocompromised
non-malignant

Autologous
inherently immunocompromised
from chemo solid tumor

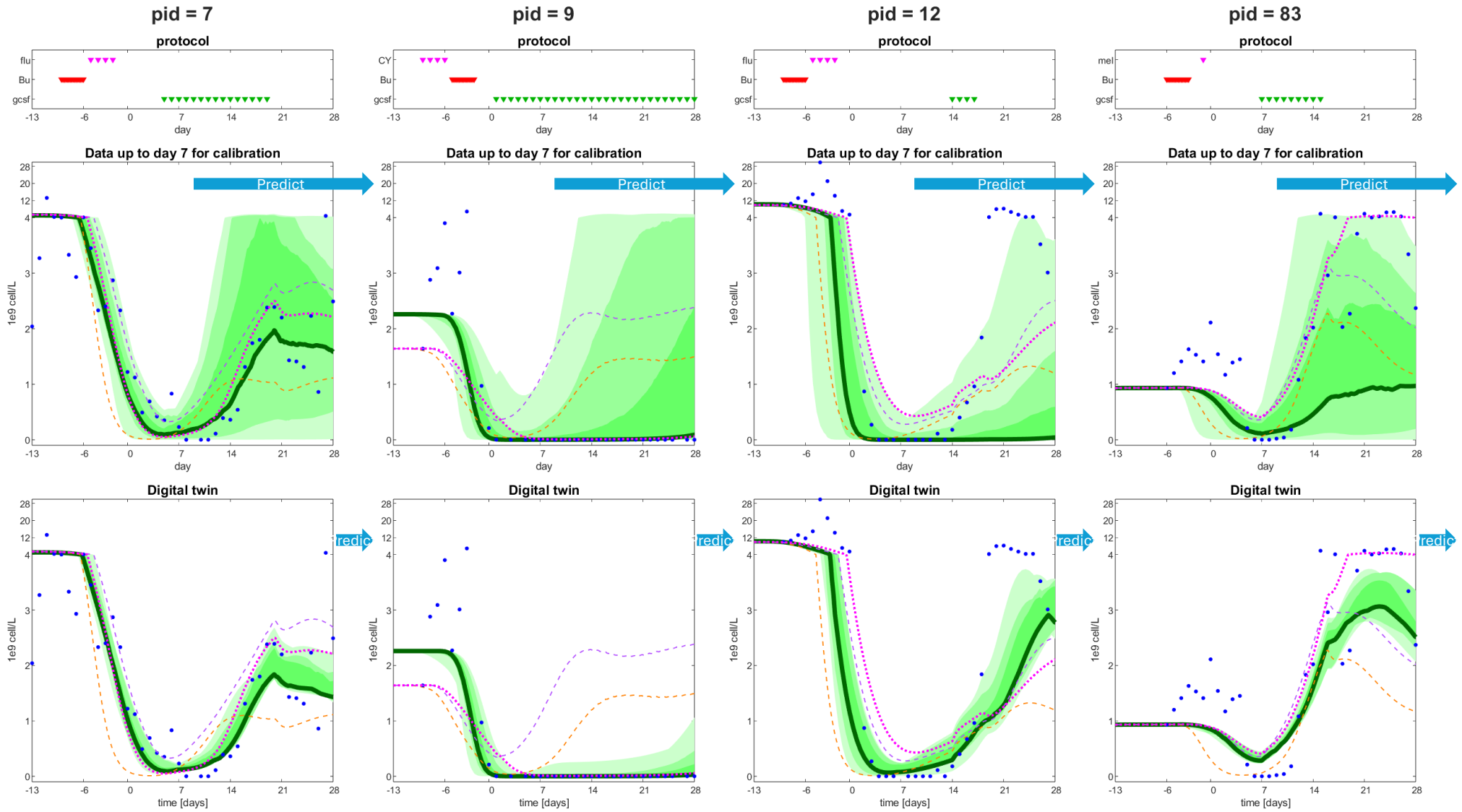
Autologous
inherently immunocompromised
non-malignant



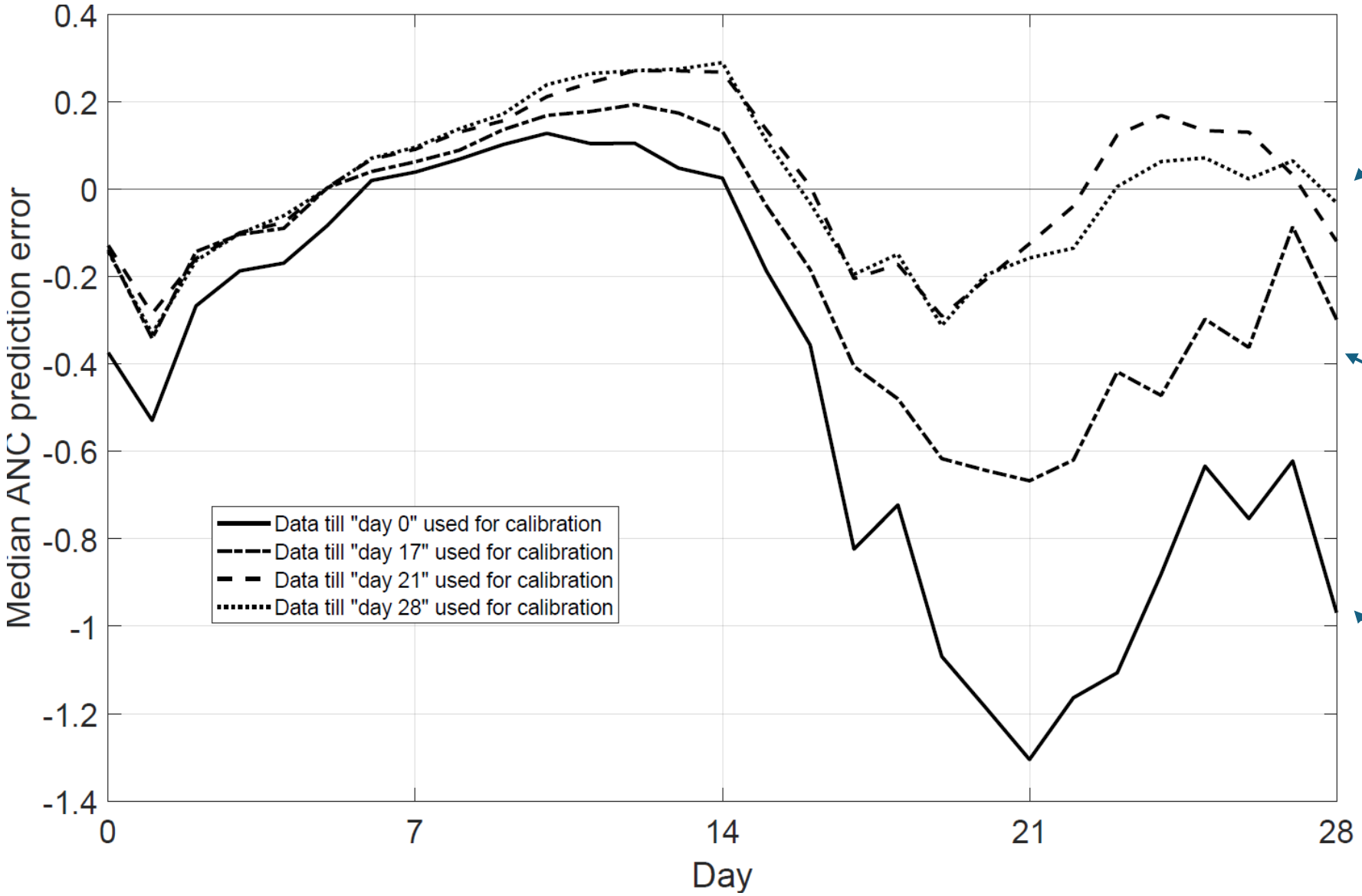
Representative patient predictions

“Useful” Digital Twin

“True” Digital Twin



Prediction error for “Digital twins” of different quality and usefulness



“True” Digital Twin
Accurate but less useful for patient

Optimal balance of accuracy and usefulness
“Useful” Digital Twin

“Pre-treatment” Digital Twin
Leveraging data from patient medical history

TPA

Target Pharmacology Assessment

Comparison with QSP

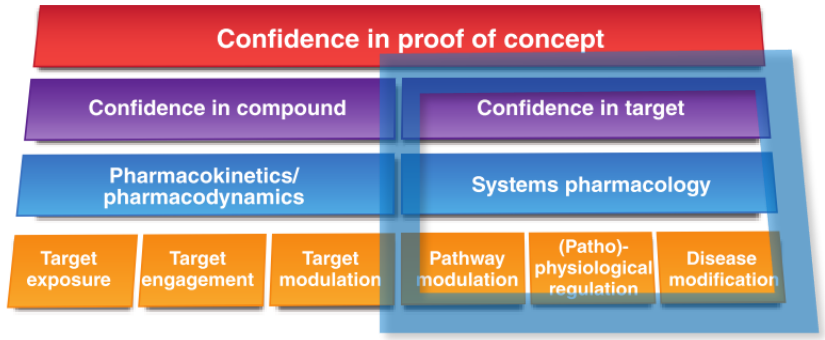


Figure 2 The relationship between pharmacokinetics/pharmacodynamics ("three pillars of survival"[11]) and systems pharmacology as parallel approaches to tackle attrition due to insufficient efficacy in proof-of-concept–phase II trials.

QSP & TPA

QSP = Mechanistic mathematical modelling approach to predict the effect of target modulation on clinical outcomes

- **Build for indications of high interest**
- **End to end application**

TPA = A computational approach centered around a pharmacodynamic (PD or QSP) model for the of target biology and clinical outcomes linked with PBPK

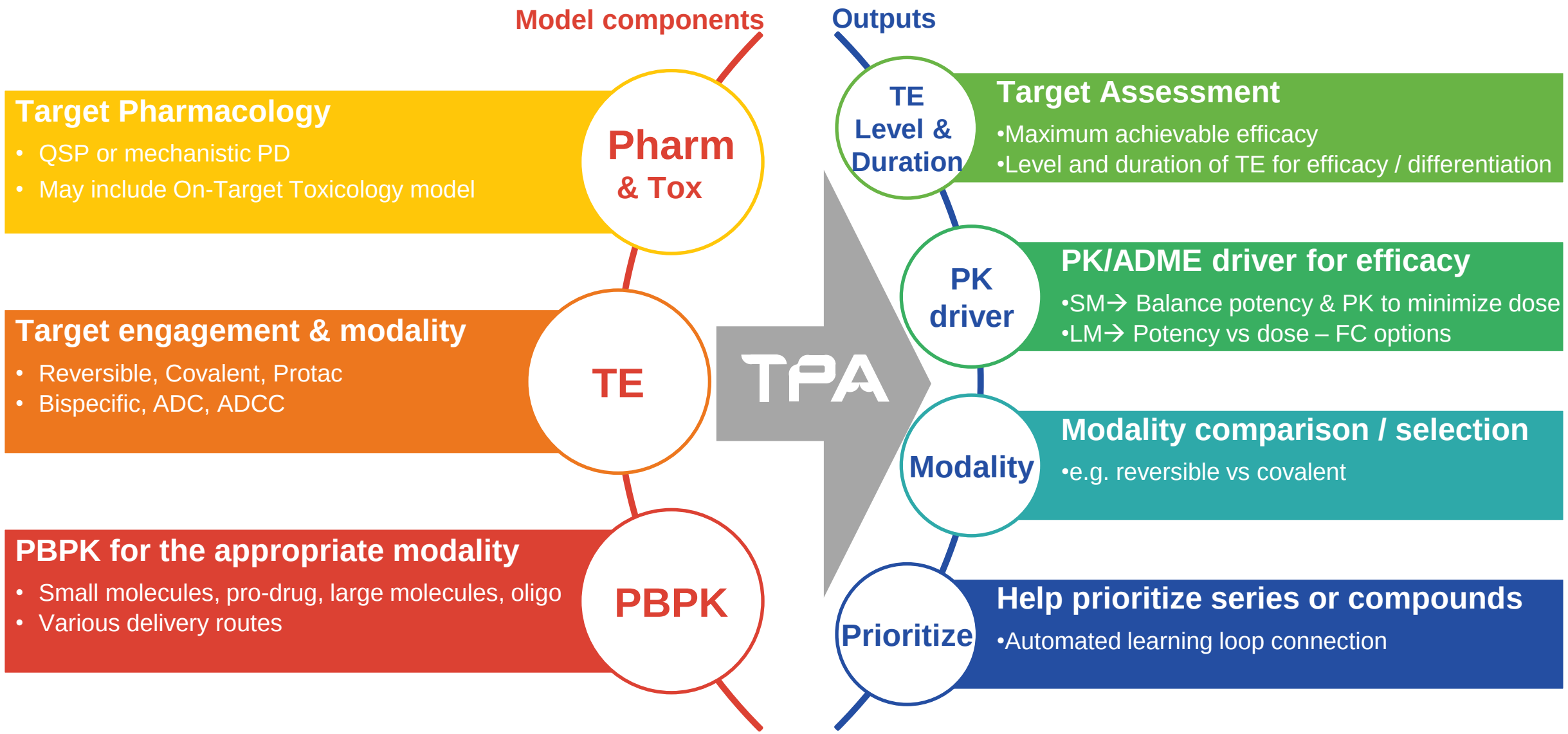
+ Large-scaled exploration of virtual profiles to identify optimal molecular and/or compound properties needed for efficacy

+ Machine learning assessment of target biology to identify risks and propose mitigating strategies to biology and medicinal chemistry

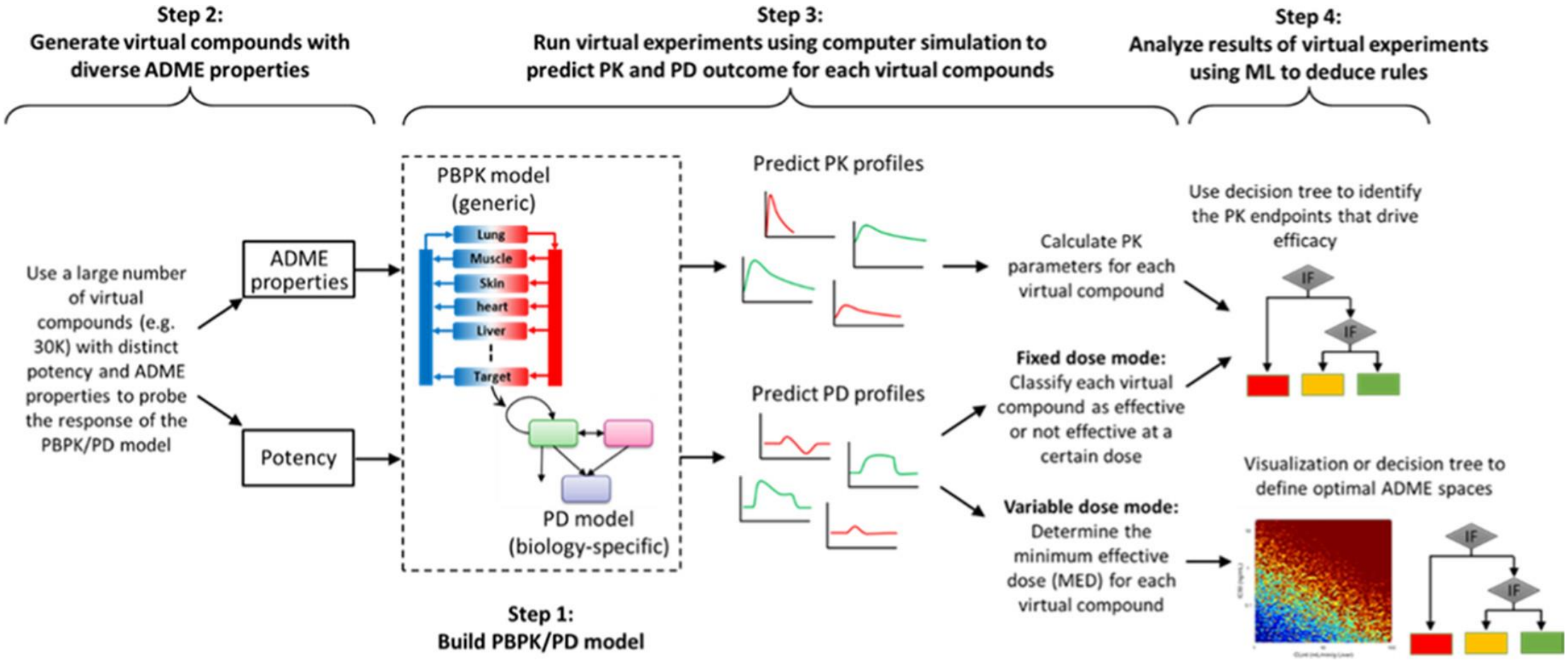
TPA = "QSP lite" applied to chemistry

- **Build between during target validation**
- **Supports discovery to accelerate time to the clinic with increased probability of success**
- **Can incorporate toxicity trade-offs**
- **Applicable to all modalities**

TPA model components and outputs



Target Pharmacology Assessment (TPA) - Right PK for the Right Target



Chen EP, Bondi RW, Michalski PJ. Model-based Target Pharmacology Assessment (mTPA): An Approach Using PBPK/PD Modeling and Machine Learning to Design Medicinal Chemistry and DMPK Strategies in Early Drug Discovery. J Med Chem. 2021 Mar 25;64(6):3185-3196. doi: 10.1021/acs.jmedchem.0c02033. Epub 2021 Mar 15. PMID: 33719432.

Chen EP, Bondi RW, Zhang C, Price DJ, Ho MH, Armacost KA, DeMartino MP. Applications of Model-Based Target Pharmacology Assessment in Defining Drug Design and DMPK Strategies: GSK Experiences. J Med Chem. 2022 May 12;65(9):6926-6939. doi: 10.1021/acs.jmedchem.2c00330. Epub 2022 May 2. PMID: 35500041.

Challenges and Opportunities

Focus on AI / ML

Types of Data and Knowledge used in modeling

Big Data

- *Omics data*
- *All (most) proteins, genes, in test system*
- *Databases*
- *Sensor data*

- Comprehensive
- Structured

Big Knowledge

- *Published data and knowledge*
- *Known physics, chemistry, biology*
- *Homeostasis*

- Peer reviewed
- Unstructured
- Captures knowledge

Targeted Data

- *High precision data on select measurements*
- *e.g. drug and biomarker*
- *In-vivo studies (e.g. PK)*
- *In-vitro studies*

- High accuracy
- Focused on most relevant measurements

Data and Knowledge types - Expectations

Big Data

Big Knowledge

Targeted Data

Data modeling
(e.g. AI / ML)

Mechanistic modeling
(e.g. QSP – PBPK)

Pharmacometrics
(e.g. PK PK/PD)

Correlation
New hypothesis

Understanding
Causality Confidence

Evidence
Validate hypothesis

Data first

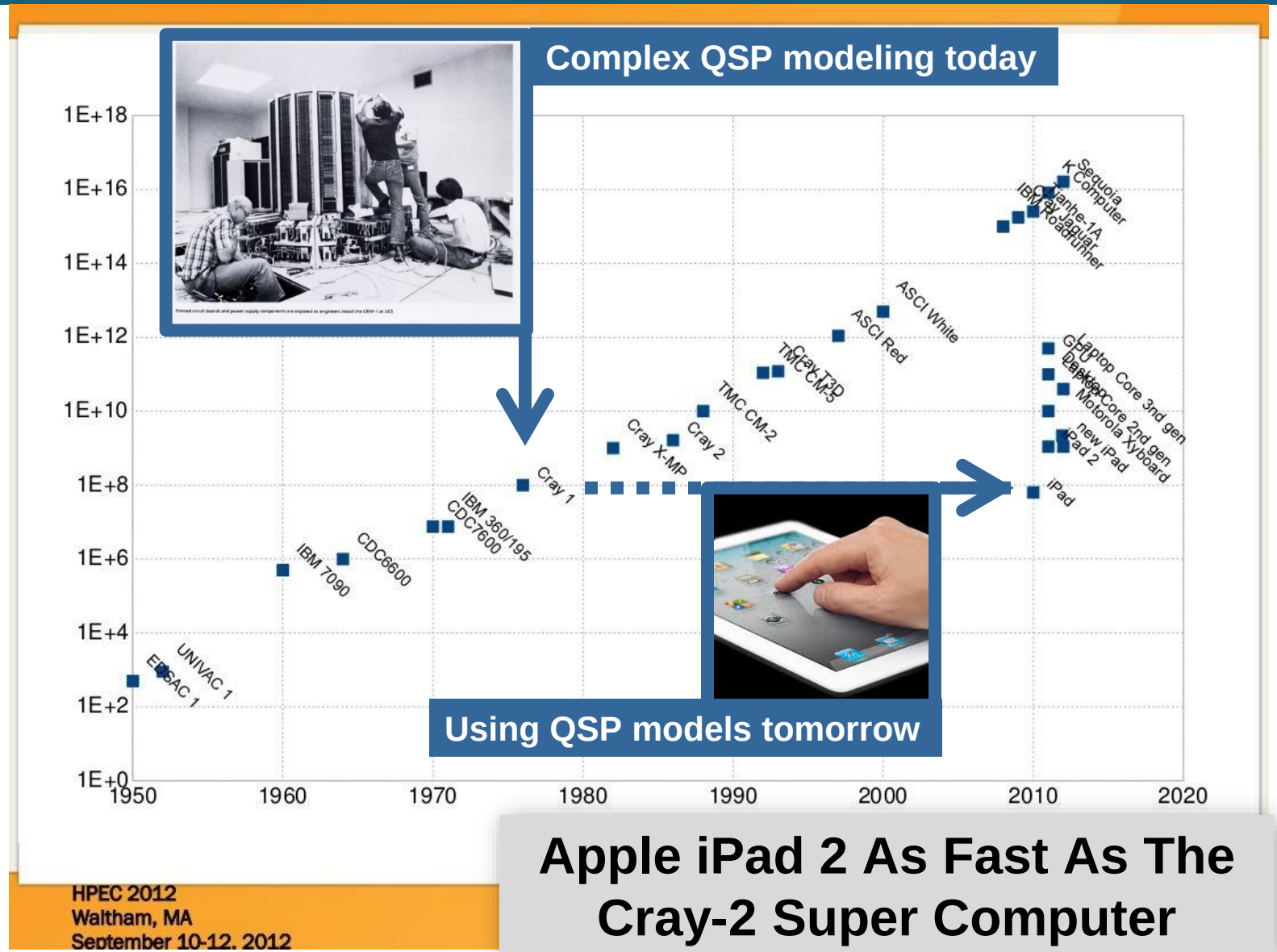
Model first

Experiment first

How can AI / ML be leveraged in QSP

	Why AI / ML?	AI / ML Approaches
Faster	Build model faster	• NLP, Network inference, Causal network inference, Code faster
	Run model faster (VP generation, GSA)	• Model (forward) surrogates (ML substitute for a ODE model) *(e.g. Regression methods, Gaussian processes, Neural networks)* • Model reduction algorithms
	Identify valid VP's faster	• Inverse surrogates (ML to generate viable VP's) *(e.g. Normalizing flows, Generative Adversarial Networks GANs)*
	Faster population calibration	• Advanced Bayesian Inference (e.g. MCMC extensions)
Novel	Novel correlations between VP parameters	• Traditional ML approaches on VP parameters for viable VP's
	Novel diagnostics to identify responders	• Traditional ML classifiers applied to viable VPs to predict responders
Better	Replace ODE modeling with mixed ODE + ML	• Neural ODEs *(infer ODE using ML)* • Physics Informed Neural Networks (PINN) *(Mechanistic regularization in NN)* • Universal differential equations (UDEs) *(NN embedded in ODE)*
	Integrate mechanistic modeling with 'omics	• ML models on 'omics used as input parameters for ODE and/or • ODE outputs used together with 'omics data in a ML model

Are we there yet !!!



Apple iPad 2 As Fast As The Cray-2 Super Computer

Shortage of QSP trained scientists

- Successful QSP modeling requires a multidisciplinary set of skills
- Missing / ignoring any of the skills would result in suboptimal or perhaps wrong QSP model leading perhaps to wrong decisions.
- E.g. without communication the best QSP model would not be influential, would not be trusted
- Individuals having ALL these skills are rare – most often QSP development is done in teams
- However successful QSP team members have basic skills and appreciation across all areas and are experts in one or two disciplines.

Responses by Valeriu Damian to Webinar Questions

Was the model used to optimize new candidate for the Acne compound (after the original candidate was de-prioritized), or the model was used to evaluate new candidates that were optimized by the team not using the QSP model?

- Except for the compound that was de-prioritized for all the other cases the model was used during the translational phase, supporting the clinical dose estimate. They were all compounds repurposed from other indications and considered for topical administration. There was no additional lead optimization activities performed on these compounds. The team(s) followed the model recommendations.

Is there a risk of extinction of QSP groups within pharma companies in the mid-term/long-term due to the influence of CROs, the progress of AI, or for any other reasons? In other words, do you think QSP groups (inside pharma companies) will grow or shrink in the future?

- Given the growing interest in QSP it is unlikely that QSP will be shrink – most likely it will grow. However, it is likely that QSP resources will be shifted to different lines in the organizations as everyone would want QSP modelers working in their line. AI/ML will help QSP modelers be more productive, but it will not replace them. CROs may influence the balance of activities a QSP modeler will do, shifting to some extent away from building models from scratch to checking suitability of licensed models, adding targets to existing models, revalidating with new data and of course making sure the models address in time the appropriate project team questions.

How can predictions from QSP be de-risked when working on targets for which there are no clinical data available?

- Novel targets modulate cellular processes that are most likely already in the QSP model and were validated with clinical data for other interventions. With appropriate in-vitro data this will effectively give high confidence in QSP model prediction. It is possible to the target modulates processes that were never included in the QSP model or never fully validated however, even in this case in the absence of clinical data the model would still provide the valuable input to the team if all assumptions and uncertainty are well communicated to the team.

Does ML deal with ODEs such as QSP?

- There was a NeuroODE paper a few years back that showed that the ODEs can be represented in deep learning architectures – so one can integrate ODE models and do parameter estimation using deep learning techniques and hardware. However, it is unlikely that AI/ML would follow the same workflow as QSP. QSP scientists will leverage AI/ML to improve their QSP workflow, but, if faced with the same questions as the ones QSP is trying to answer, AI/ML scientists will most likely develop different workflows better adapted to make use of AI/ML tools.

Is there training workshop for QSP?

- It is possible there is a training workshop specifically for QSP, but I am not aware. There is however a series of 4 educational webinars organized by ASCPT in September.

Great presentation! I have a question about digital twins. While I see the value of digital twins in personalized precision medicine, I am curious about their benefits in the context of a QSP disease platform and virtual population development workflow. Are there additional advantages to creating a digital copy of individual patients when we can already perform analysis in a virtual population (VPop)?

- Thank you. I see limited advantage in creating digital copies of individual patients and sample this cohort of twins for population level predictions, however I have seen this being proposed as an approach because one can argue you are sampling real patients. It may work perhaps if you have Phase III patient level data and want to predict a Phase II in the same population for a different treatment. In any case I would not look at this as the main digital twin application. I would use digital twins for precision medicine. Imagine a few years from now that a digital twin would be part of a patient medical record. Inclusion criteria for a trial could be based on the digital twin predictions … while not impossible at some point, this is a bit too far for now.

Will we be able to access the recordings?

- Yes, recordings will be made available.

Thank you, fantastic presentation!

- Thank you.

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- Grace Kang

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- William Rumsey
- Noushin Brealey
- David Fairman
- Martin Hingle

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