ASCPT

FROM MOLECULE TO PATIENT

ASCPT 2019 ANNUAL MEETING

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Strategies To Effectively Deploy Quantitative Systems Pharmacology Approaches In Clinical Development

Paolo Vicini, PhD, MBA
Vice President, Development Sciences, Kymab Ltd

ASCPT 2019 - Connecting Cell Biology to Patient Populations: Clinical Applications of Multi-Scale Systems Pharmacology

Interest in QSP Is Growing, Has Its Potential Been Fully Realized?

FROM MOLECULE TO PATIENT

CERTARA

Discovery on TARGET

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Preclinical QSP Modeling in the Pharmaceutical Industry: An IQ Consortium SurveyExamining the Current Landscape. Marjoleen J.M.A. Nijsen, Fan Wu, Loveleena Bansal, Erica Bradshaw-Pierce, Jason R. Chan, Bianca M. Liederer, Jerome T. Mettetal, Patricia Schroeder, Edgar Schuck, Alice Tsai, Christine Xu, Anjaneya Chimalakonda, Kha Le, Mark Penney, Brian Topp, Akihiro Yamada, Mary E. Spilker CPT Pharmacometrics Syst Pharmacol. 2018 Mar; 7(3): 135–146.

Objective of Medicine Development: Identify A Therapeutic Window

FROM MOLECULE TO PATIENT

Dose

↓

Pharmacokinetics

↓

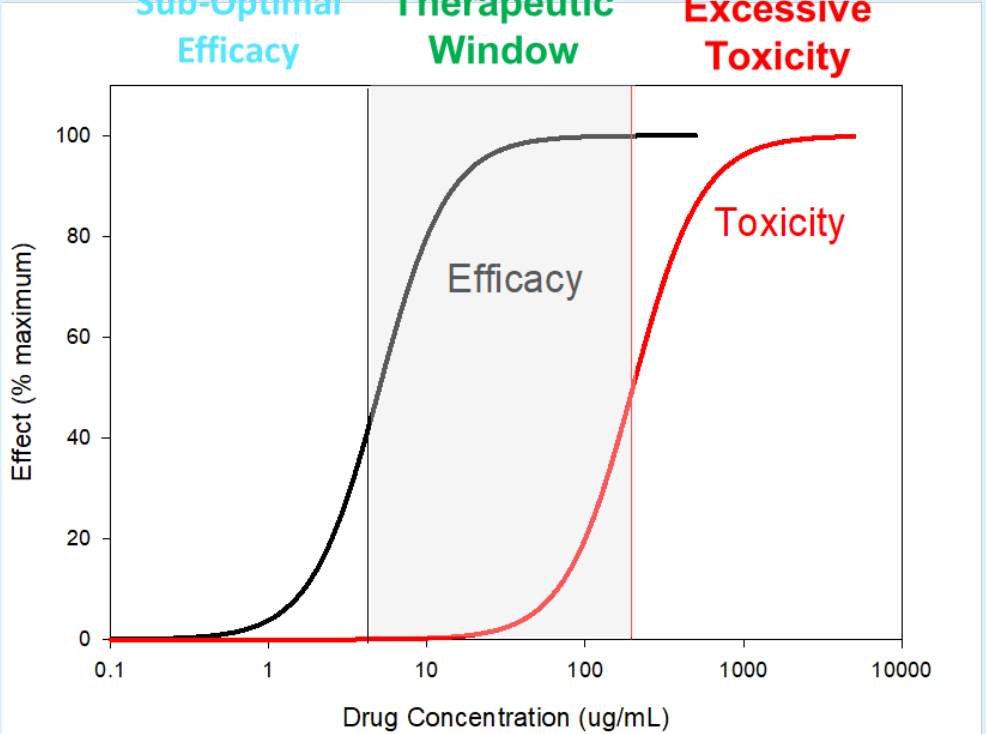
Concentration

↓

Pharmacodynamics

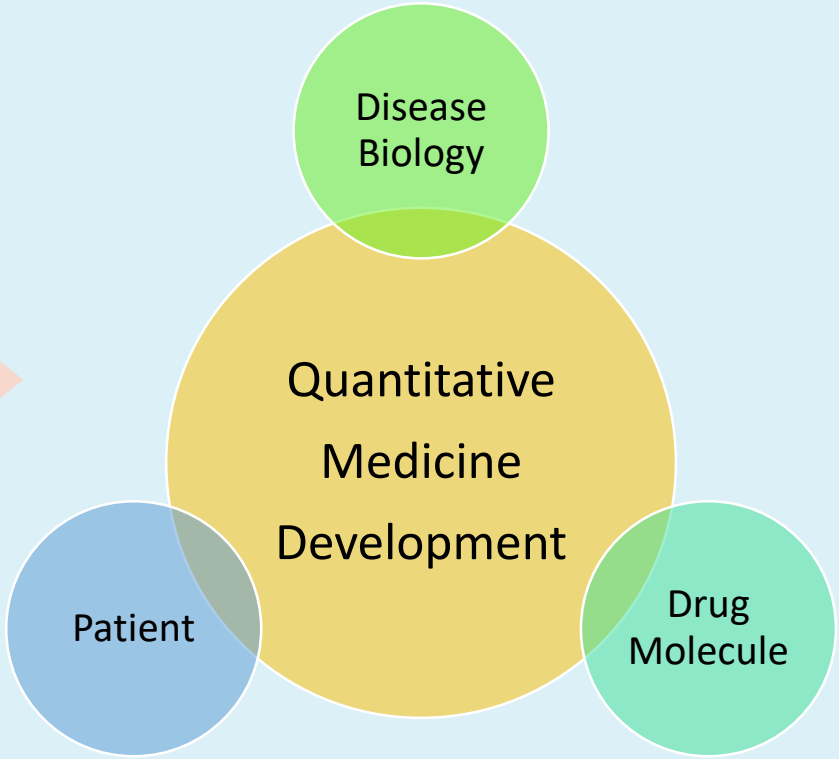
↓

Effect



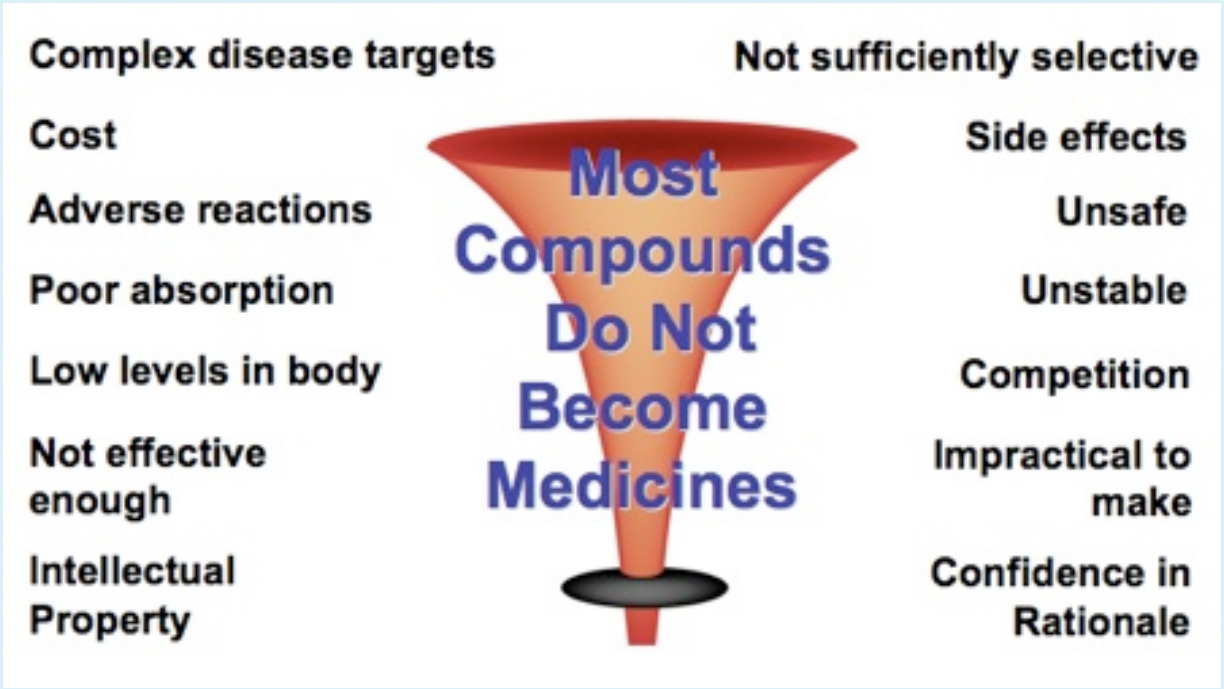
The Science of Drug Development

FROM MOLECULE TO PATIENT



Drug Development Is Fraught with Risks, Only Some Well Understood

FROM MOLECULE TO PATIENT

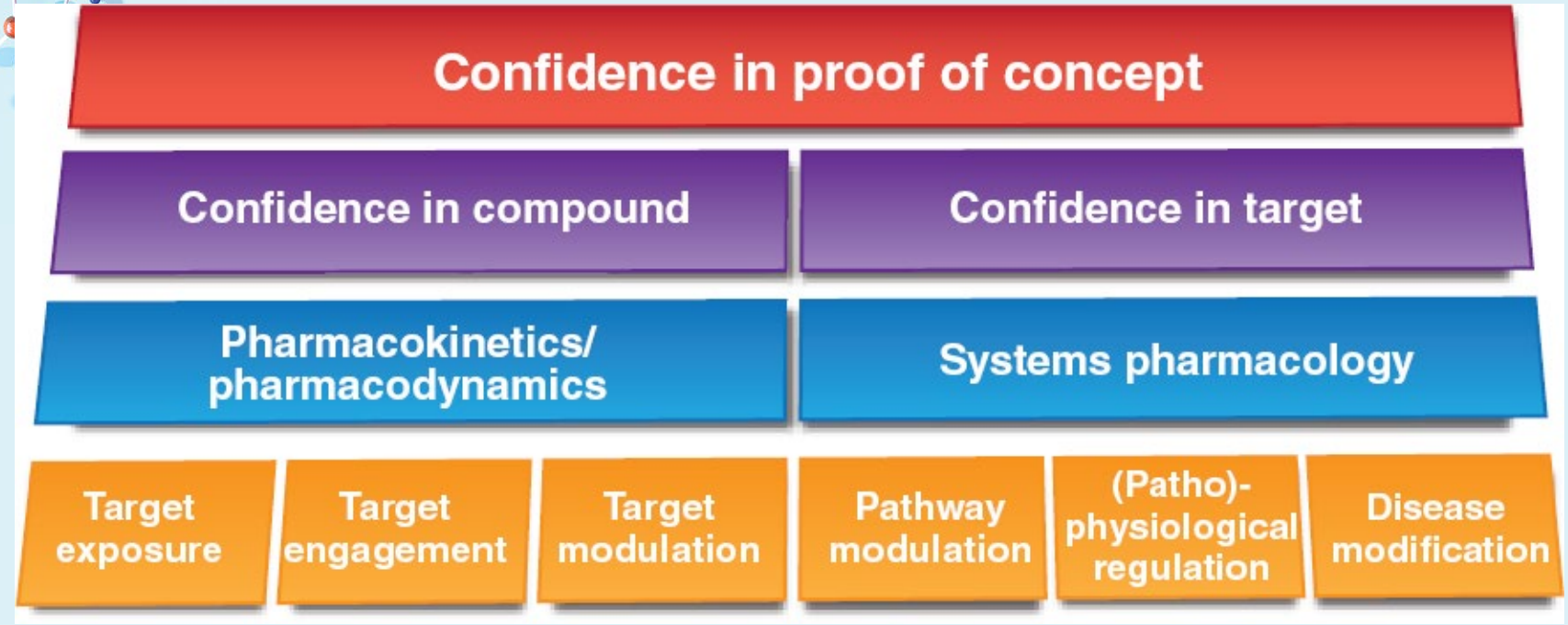


http://en.wikibooks.org/wiki/Structural_Biochemistry/Outside_the_Cell

PK-PD and Systems Pharmacology

Parallel approaches to tackle attrition in pharmaceutical R&D

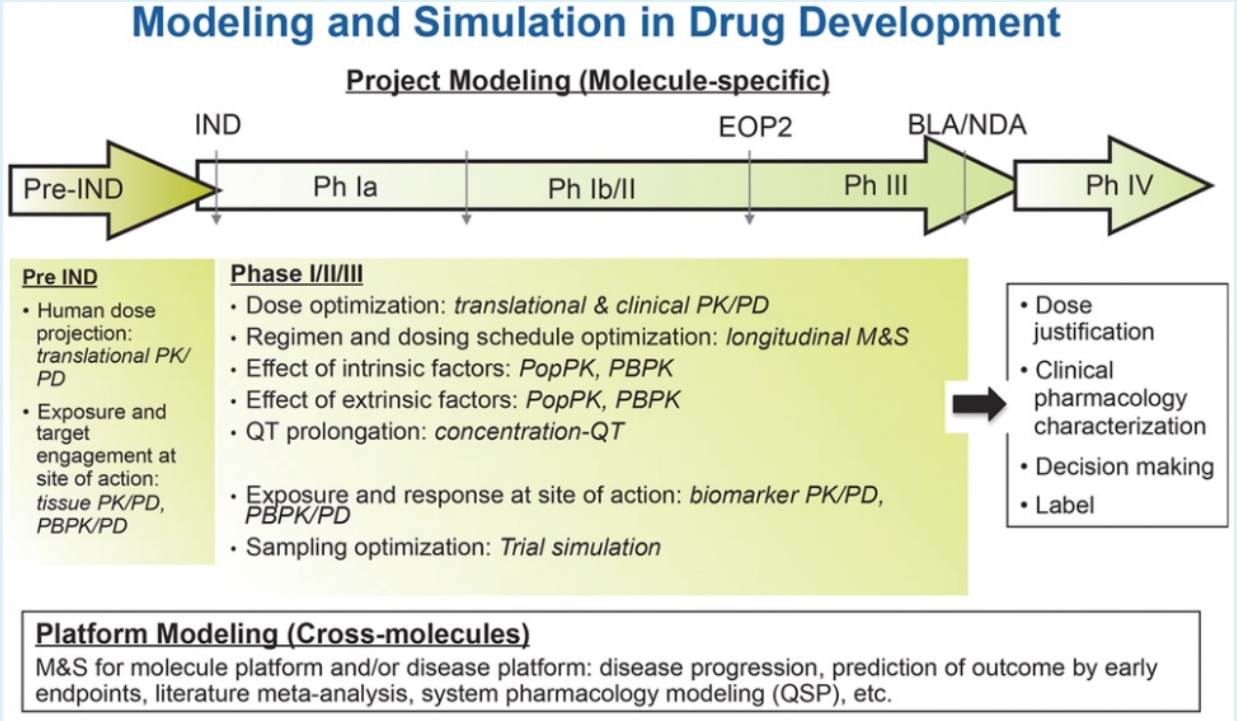
FROM MOLECULE TO PATIENT



Systems pharmacology for drug discovery and development: paradigm shift or flash in the pan? Vicini P, van der Graaf PH. Clin Pharmacol Ther. 2013 May;93(5):379-81. Used by permission.

Integrated, Quantitative Approaches to Development

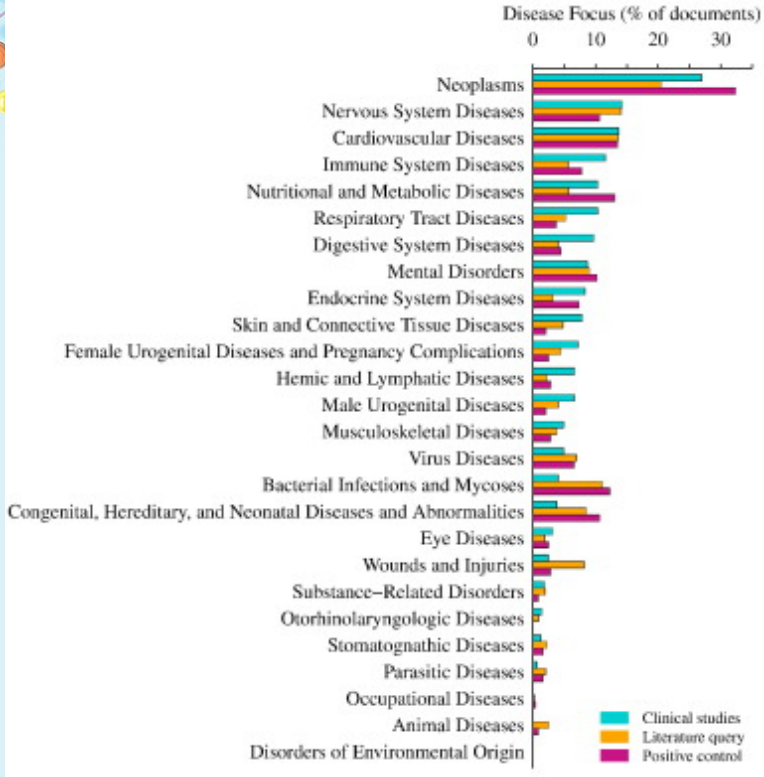
FROM MOLECULE TO PATIENT



Challenges and Opportunities in Dose Finding in Oncology and Immuno-oncology. Ji Y, Jin JY, Hyman DM, Kim G, Suri A. Clin Transl Sci. 2018 Feb 1. doi: 10.1111/cts.12540.

Clinical Trials and QSP Modelling

FROM MOLECULE TO PATIENT



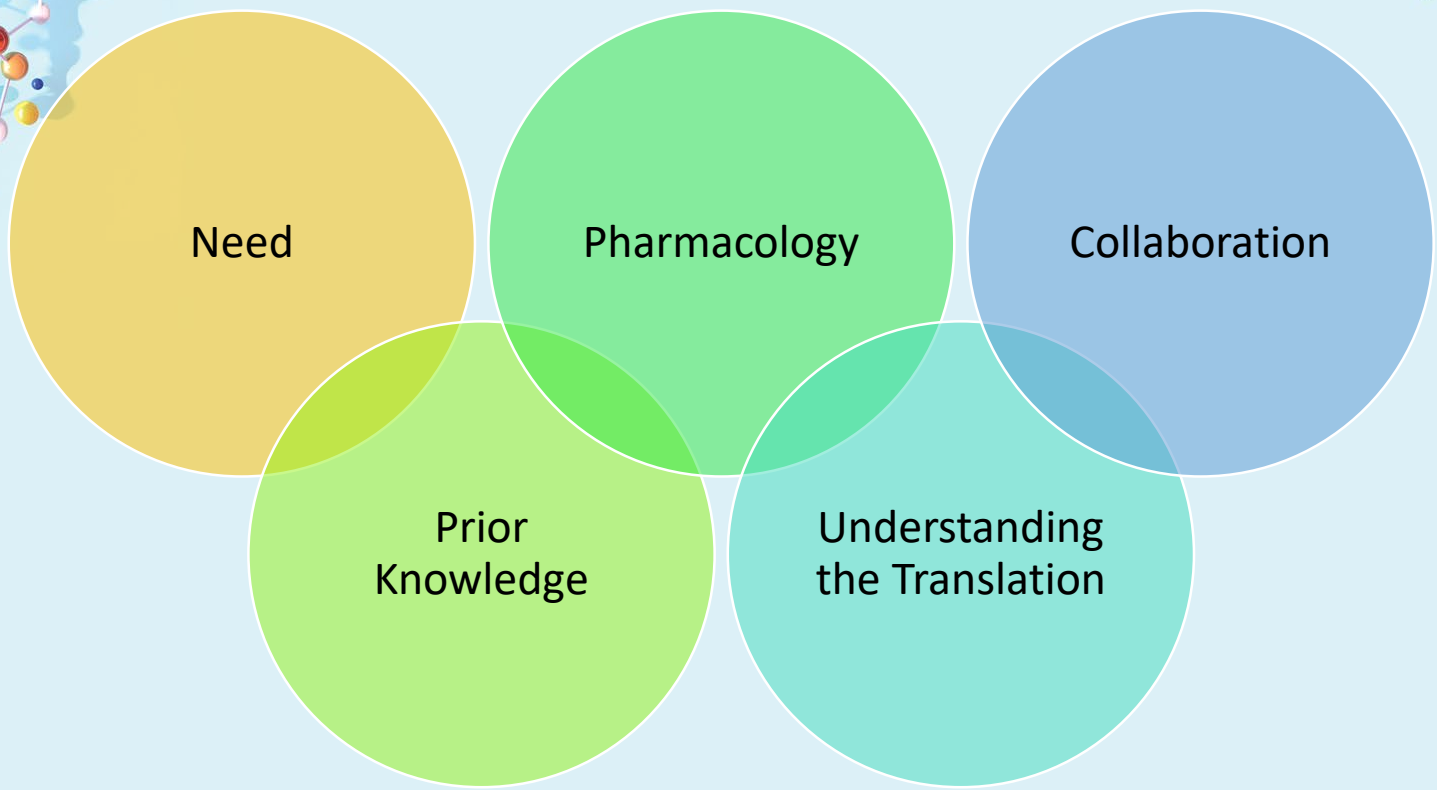
Corpus	n_t	n_d
Clinical studies	177,609	147,235
Modelling literature	215,097	85,676
Positive control literature	687	244

total number of documents; nd number of documents labelled with a disease.
a
clinicaltrials.gov.
b
Medline — text mining query for models.
c
BioModels database.

The promises of quantitative systems pharmacology modelling for drug development. V.R. Knight-Schrijver, V. Chelliah, L. Cucurull-Sanchez, N. Le Novère. Comput Struct Biotechnol J. 2016; 14: 363–370.

Getting the Balance Right

FROM MOLECULE TO PATIENT



Methodologies for Quantitative Systems Pharmacology (QSP) Models: Design and Estimation. B Ribba, HP Grimm, B Agoram, MR Davies, K Gadkar, S Niederer, N van Riel, J Timmis, PH van der Graaf. CPT Pharmacometrics Syst Pharmacol. 2017 Aug; 6(8): 496–498.

Roadmap to Success for the QSP Model Deliverable

FROM MOLECULE TO PATIENT

Cost: *Frame early expectation that M&S can be a significant endeavour in terms of both time invested and cost required, but do not lose sight of return on investment*

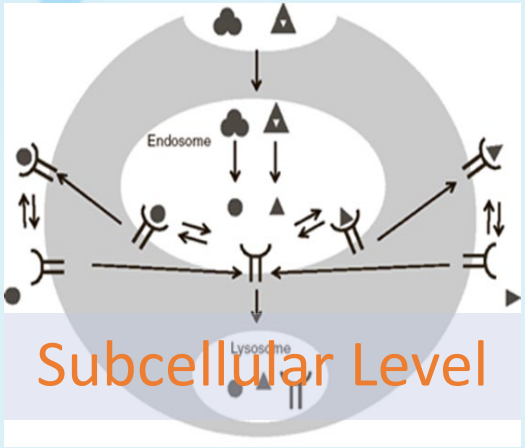
Value Added: *Clarify early on what the investment's added value should be, by setting M&S up to answer relevant questions that are as crisp and directed as possible*

Check In: *The M&S team must make a sustained effort to frequently communicate with, and provide updates to, all the stakeholders (e.g. project team) over time*

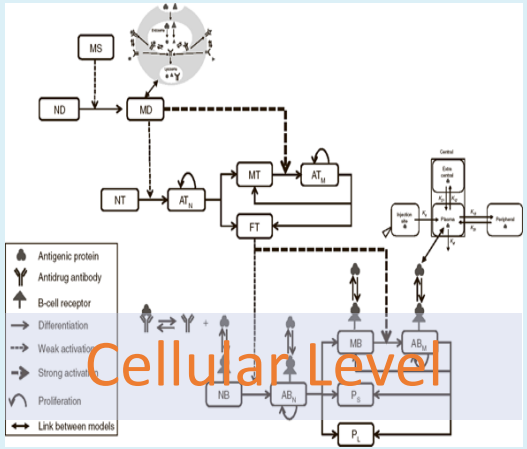
Quick Wins: *Try and use preliminary versions of the model to continuously propose novel hypotheses, design experiments and otherwise keep stakeholders engaged*

Systems Pharmacology of Biotherapeutic Immunogenicity

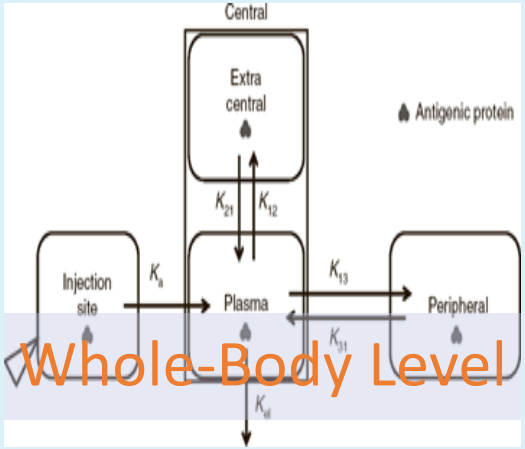
FROM MOLECULE TO PATIENT



Subcellular Level



Cellular Level



Whole-Body Level

A mechanistic, multiscale mathematical model of immunogenicity for therapeutic proteins: part 1-theoretical model. Chen X, Hickling TP, Vicini P. CPT Pharmacometrics Syst Pharmacol. 2014 Sep 3;3:e133.

A mechanistic, multiscale mathematical model of immunogenicity for therapeutic proteins: part 2-model applications. Chen X, Hickling TP, Vicini P. CPT Pharmacometrics Syst Pharmacol. 2014 Sep 3;3:e134.

Case Study: Simulate Human Immunogenicity

FROM MOLECULE TO PATIENT

Protein-specific parameters

1. Number of T-epitopes
2. Binding affinity of T-epitopes
3. Number of B-epitope
4. Binding affinity of B-epitope

…

Host-specific parameters

5. MHC-II allele genotype
6. Naïve T cell number
7. Naïve B cell number
8. Drug Clearance rate

…

MHC-II allele	Epitope 1 binding affinity (nM)	Epitope 2 binding affinity (nM)
DRB1*04:01	123	85
DRB1*04:03	78.52	147.85
DRB1*04:04	180	38
DRB1*04:07	124.73	104.16
DRB1*04:11	57.44	101.5
DRB1*07:01	75	77
DRB1*08:02	306	292
DRB1*08:11	112.43	4000
DRB1*11:01	317	293
DRB1*14:04	53.7	4000
DRB1*15:01	148	4000
Rest of DRB1 alleles	4000	4000

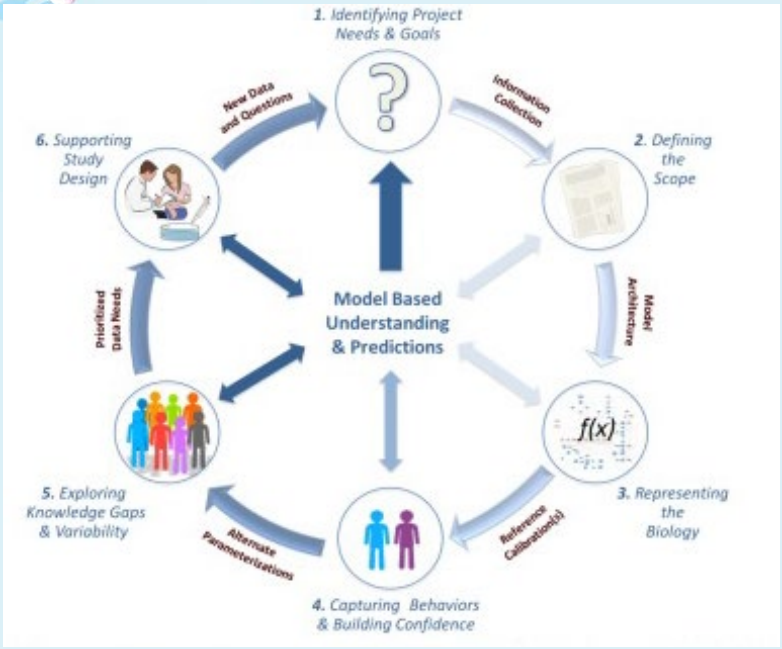
MHC-II allele	Allele frequency in North America
DRB1*04:01	0.089
DRB1*04:03	0.053
DRB1*04:04	0.036
DRB1*04:07	0.085
DRB1*04:11	0.15
DRB1*07:01	0.0083
DRB1*08:02	0.069
DRB1*08:11	0.0015
DRB1*11:01	0.0436
DRB1*14:04	0.00075
DRB1*15:01	0.0083
Rest of DRB1 alleles	0.46

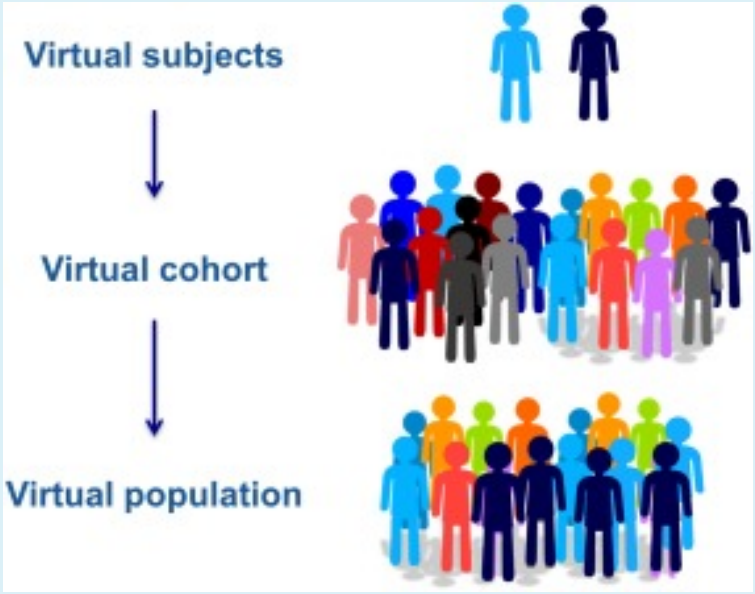
19

A Mechanistic, Multiscale Mathematical Model of Immunogenicity for Therapeutic Proteins: Part 2—Model Applications. X Chen, T P Hickling and P Vicini. CPT Pharmacometrics Syst. Pharmacol. (2014) 3, e134

The Community has Defined Processes for QSP Model Building

FROM MOLECULE TO PATIENT



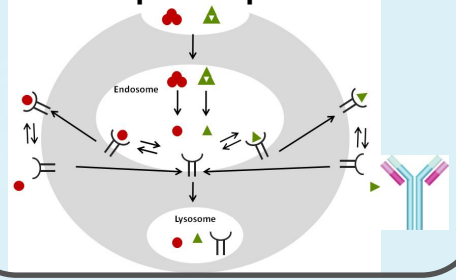


A Six-Stage Workflow for Robust Application of Systems Pharmacology. Gadkar K, Kirouac DC, Mager DE, van der Graaf PH, Ramanujan S. CPT Pharmacometrics Syst Pharmacol. 2016 May;5(5):235-49.

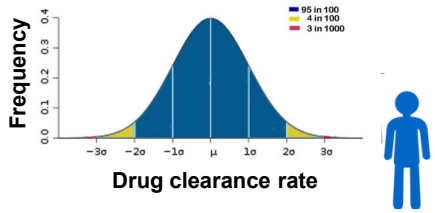
Data Integration

FROM MOLECULE TO PATIENT

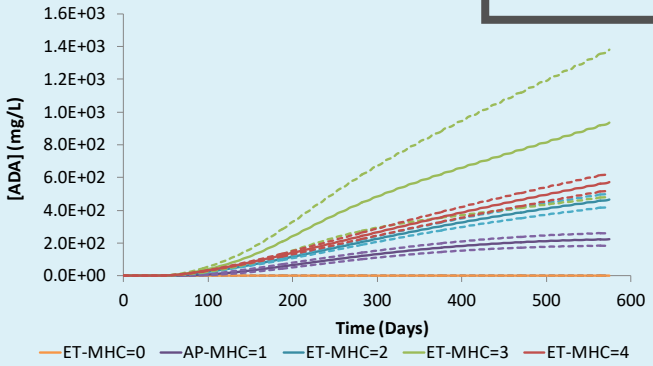
Protein-specific parameters

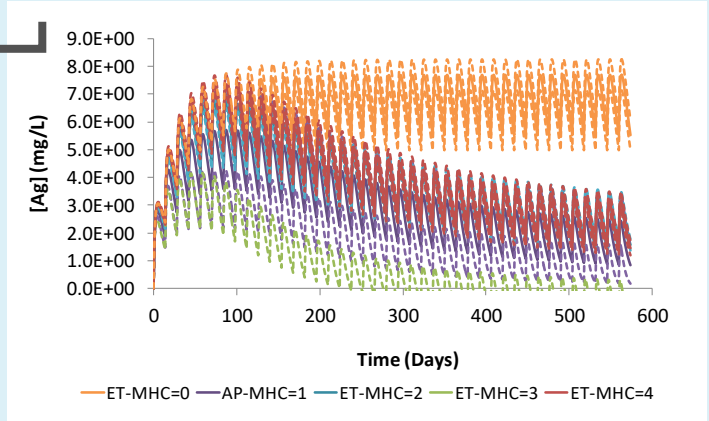


Host-specific parameters



Model simulation

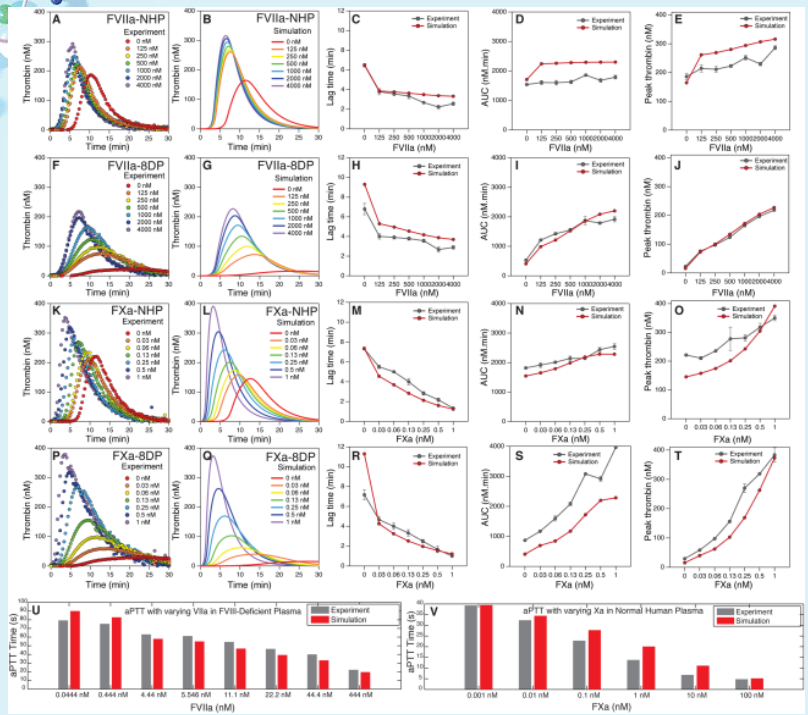


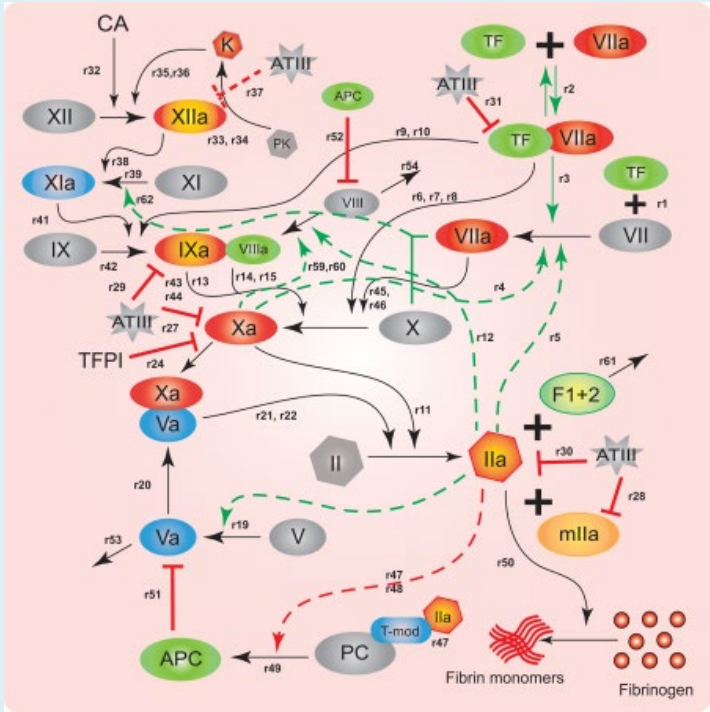


Mechanistic models for hypothesis generation

System Pharmacology of the Coagulation Cascade

FROM MOLECULE TO PATIENT

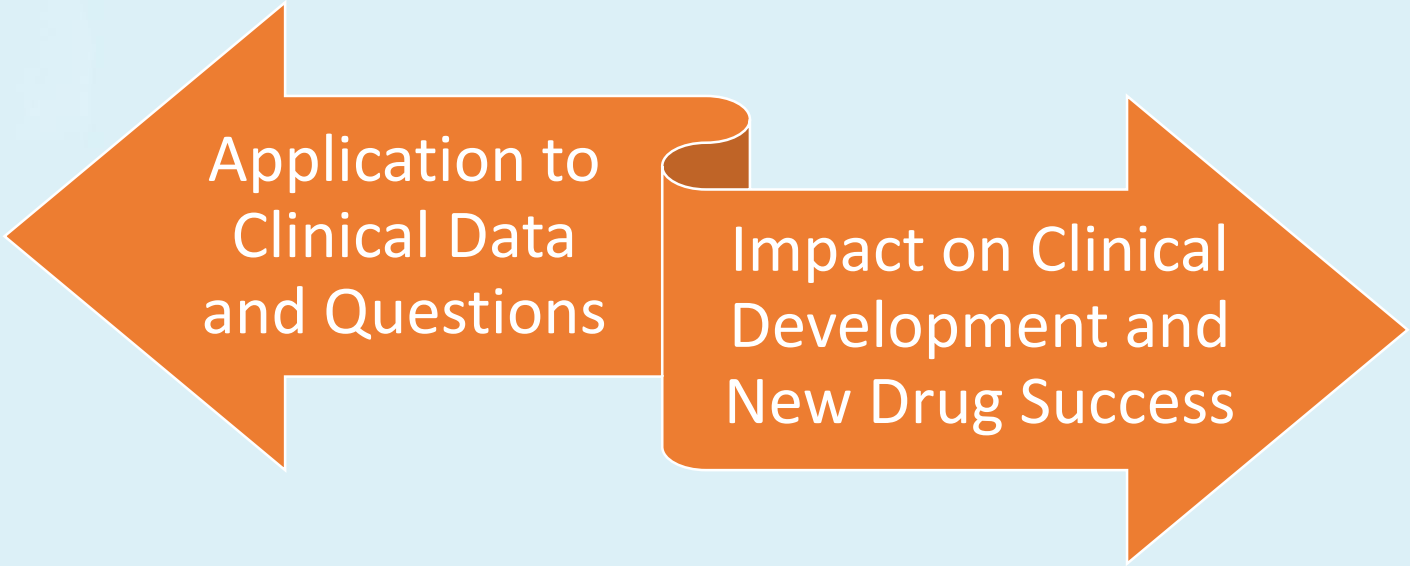




Using a Systems Pharmacology Model of the Blood Coagulation Network to Predict the Effects of Various Therapies on Biomarkers. Nayak S, Lee D, Patel-Hett S, Pittman DD, Martin SW, Heatherington AC, Vicini P, Hua F. CPT Pharmacometrics Syst Pharmacol. 2015 Jul;4(7):396-405.

Application Is Not Impact: QSP Models Cannot Replace Experimentation

FROM MOLECULE TO PATIENT

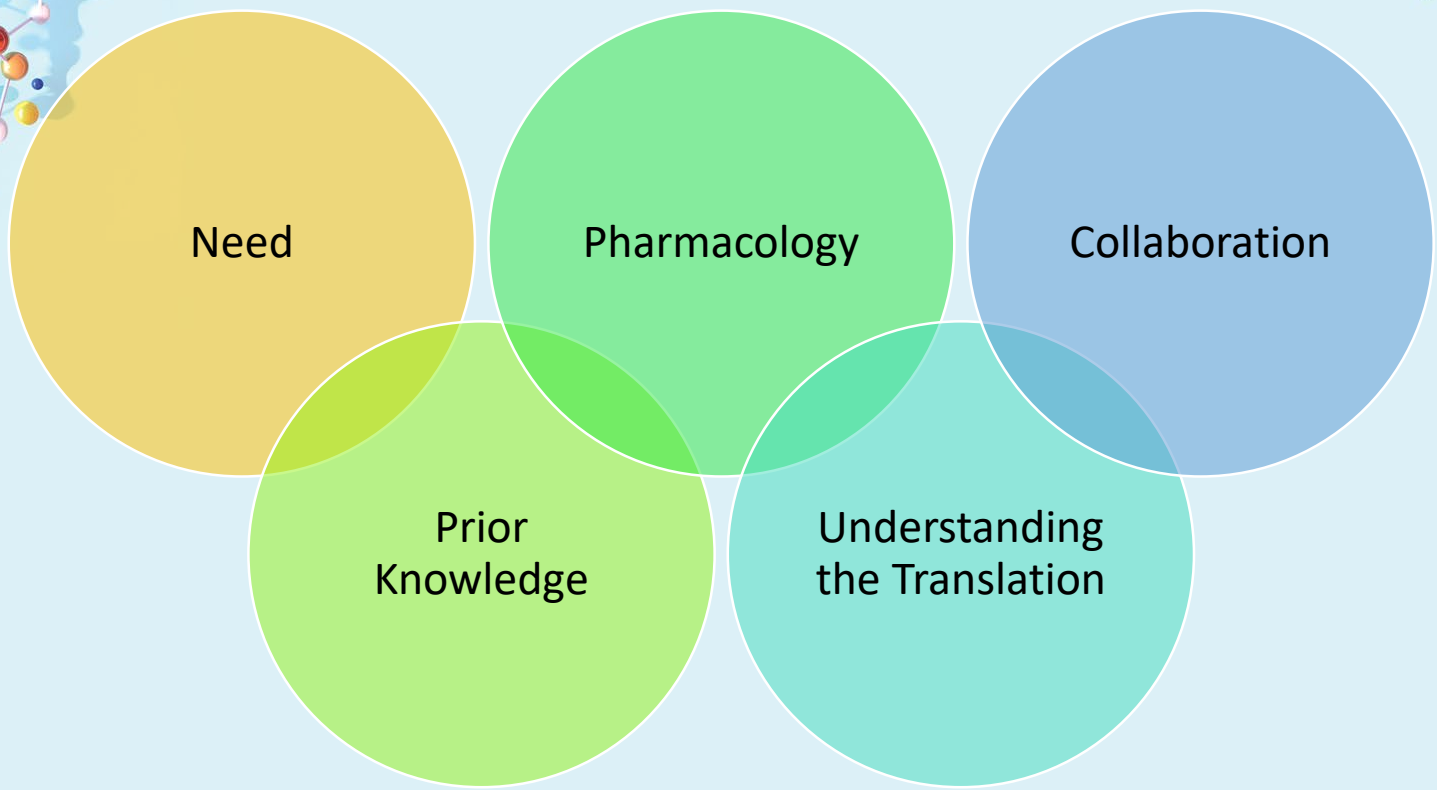


Clinical experimentation is performed on the intact system
What we exclude from the model is as important as what we include

Quantitative Systems Pharmacology (QSP) as an Integral Component of Clinical Development: Case Studies. Presenters: Piet van der Graaf, Richard Bertz, Gabriel Helmlinger, Wayne Chu. Moderator: CJ Musante. May 5, 2017.

Getting the Balance Right

FROM MOLECULE TO PATIENT



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Sometimes Emphasis on Technology Gets in the Way of QSP's Goals

FROM MOLECULE TO PATIENT

Discovery – Best home for QSP?

- Target properties and translational PK/PD

Development – QSP's role is being defined

- Pharmacometrics, trial simulation

The overall goal should not be to "raise the bar for few", but to "shift the baseline" for the whole pharma sector

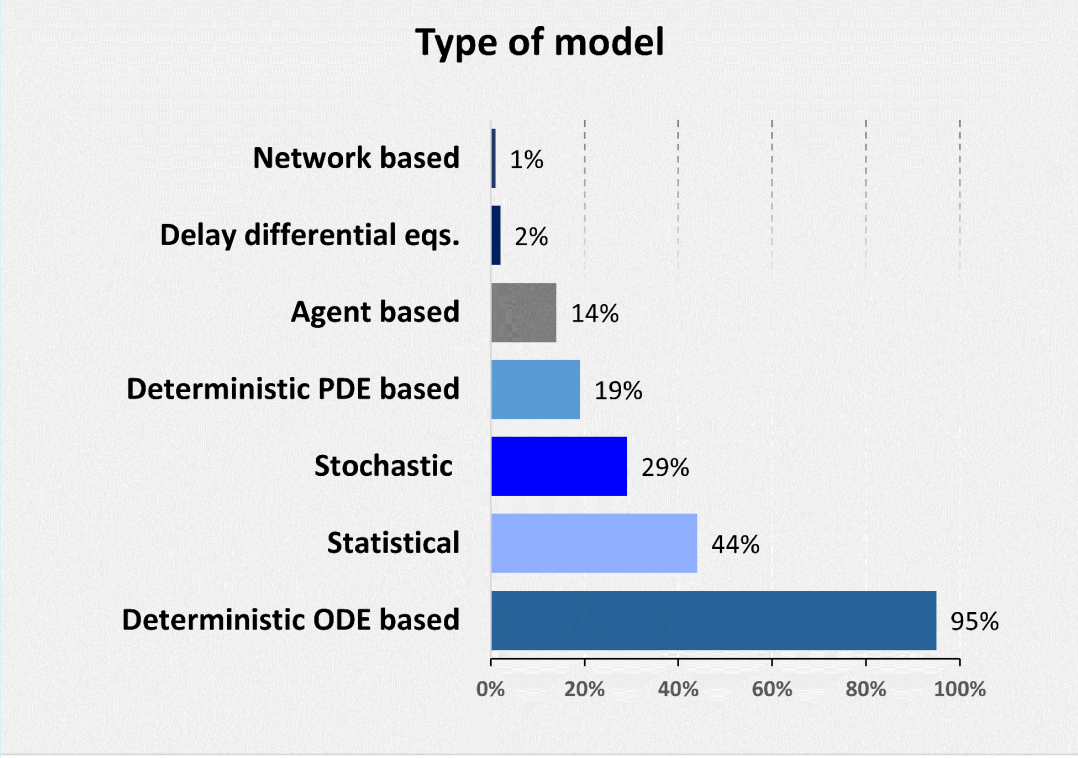
Model-Informed Drug Discovery and Development: Current Industry Good Practice and Regulatory Expectations and Future Perspectives. Marshall S, Madabushi R, Manolis E, Krudys K, Staab A, Dykstra K, Visser SAG. CPT Pharmacometrics Syst Pharmacol. 2019 Feb;8(2):87-96.

Regulatory Impact is Under Discussion and Evolving

QSP in development is often invoked when clinical data interpretation is equivocal → Can it improve clinical trial results?

Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation EFPIA MID3 Workgroup, SF Marshall, R Burghaus, V Cosson, SYA Cheung, M Chenel, O DellaPasqua, N Frey, B Hamrén, L Harnisch, F Ivanow, T Kerbusch, J Lippert, PA Milligan, S Rohou, A Staab, JL Steimer, C Tornøe, SAG Visser. CPT Pharmacometrics Syst Pharmacol. 2016 Mar; 5(3): 93–122.

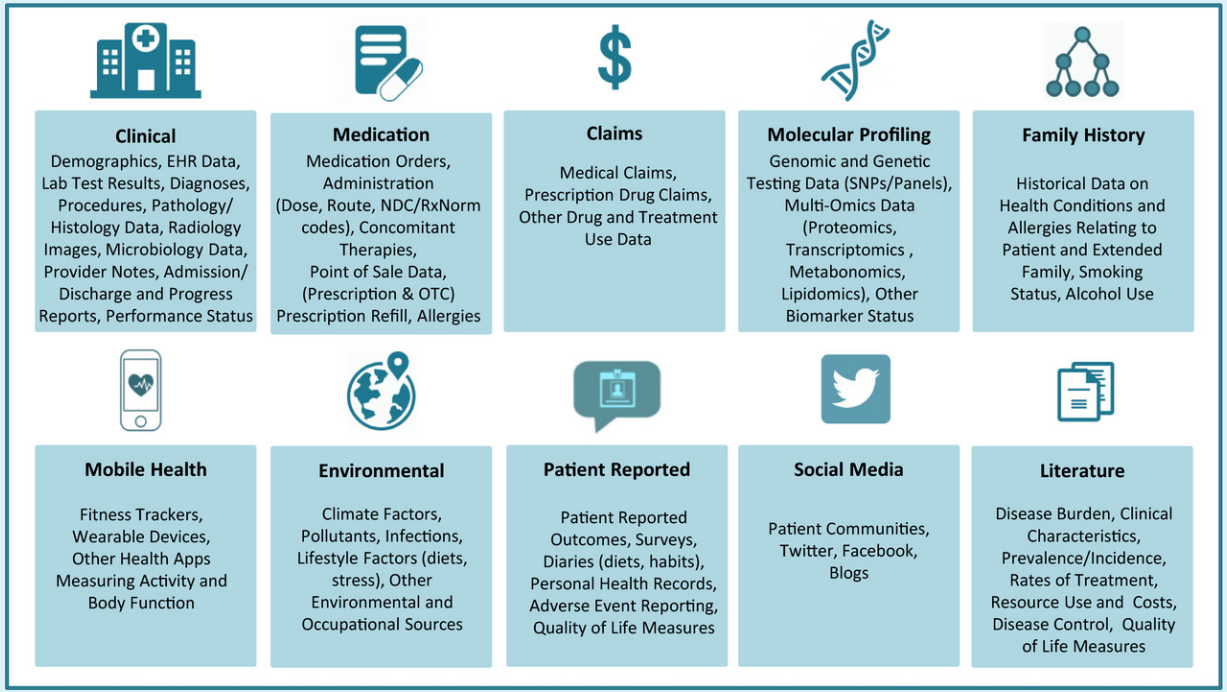
Relative Uniformity of Tools



A Survey of Software Tool Utilization and Capabilities for Quantitative Systems Pharmacology: What We Have and What We Need. Sergey Ermakov Brian J. Schmidt Cynthia J. Musante Craig J. Thalhauser. CPT Pharmacometrics Syst Pharmacol. White Paper. First published: 12 November 2018.

Sources of Data for Quantitative Approaches Are Changing Rapidly

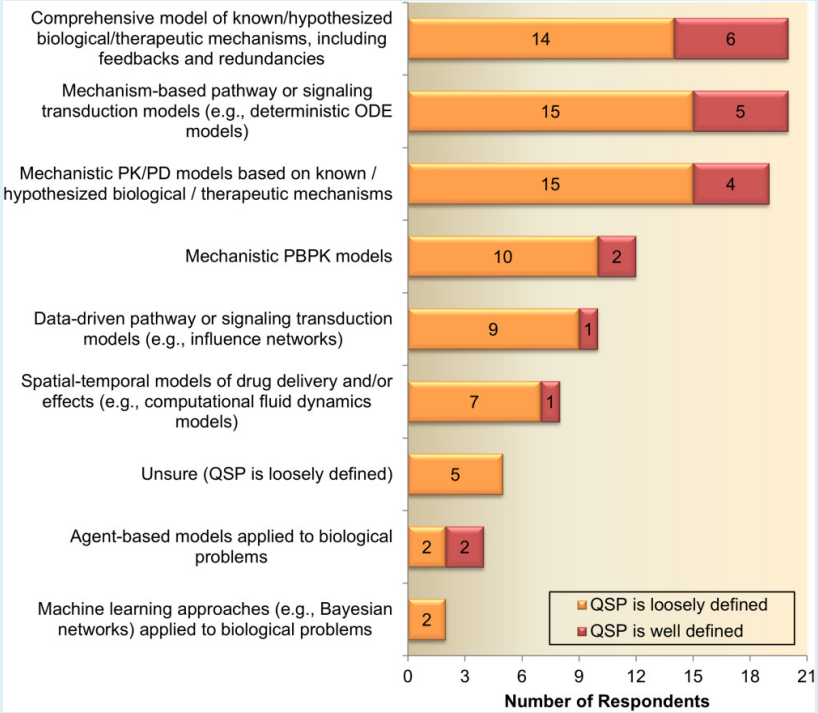
FROM MOLECULE TO PATIENT



Innovation at the Intersection of Clinical Trials and Real-World Data Science to Advance Patient Care. Swift B, Jain L, White C, Chandrasekaran V, Bhandari A, Hughes DA, Jadhav PR. Clin Transl Sci. 2018 Sep;11(5):450-460

Are Modelling Approaches Keeping Up with These Developments?

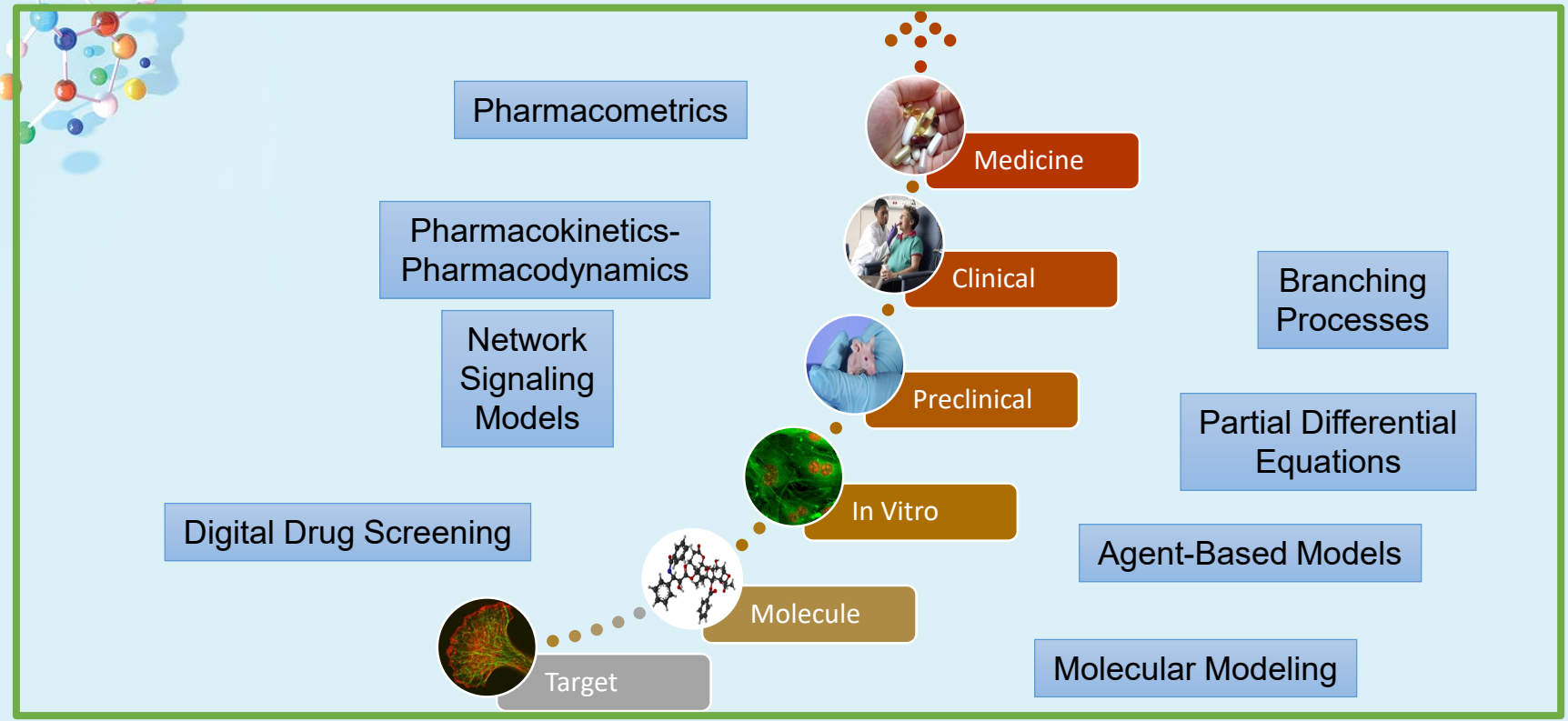
FROM MOLECULE TO PATIENT



Preclinical QSP Modeling in the Pharmaceutical Industry: An IQ Consortium Survey Examining the Current Landscape. Marjoleen J.M.A. Nijsen, Fan Wu, Loveleena Bansal, Erica Bradshaw-Pierce, Jason R. Chan, Bianca M. Liederer, Jerome T. Mettetal, Patricia Schroeder, Edgar Schuck, Alice Tsai, Christine Xu, Anjaneya Chimalakonda, Kha Le, Mark Penney, Brian Topp, Akihiro Yamada, Mary E. Spilker CPT Pharmacometrics Syst Pharmacol. 2018 Mar; 7(3): 135–146.

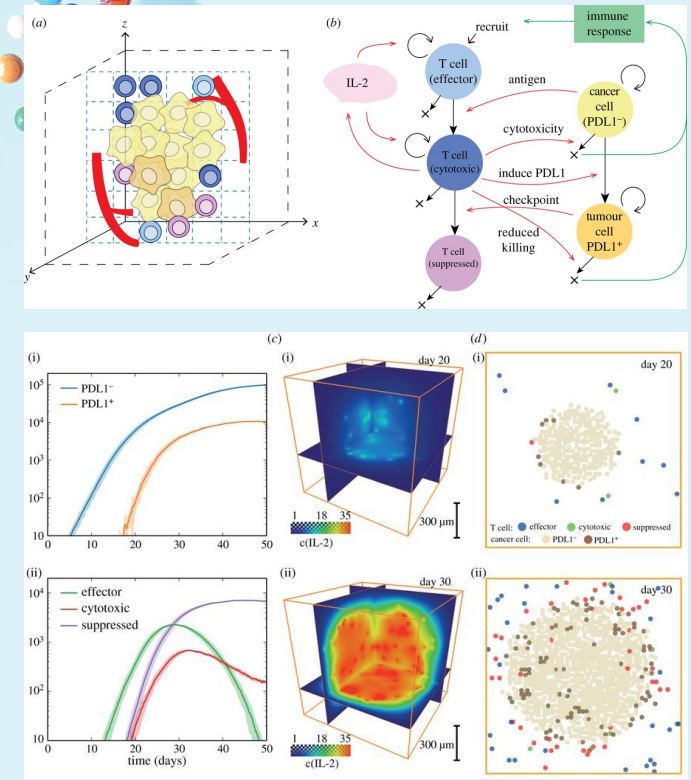
A Modular View Is Tempting, But Limiting

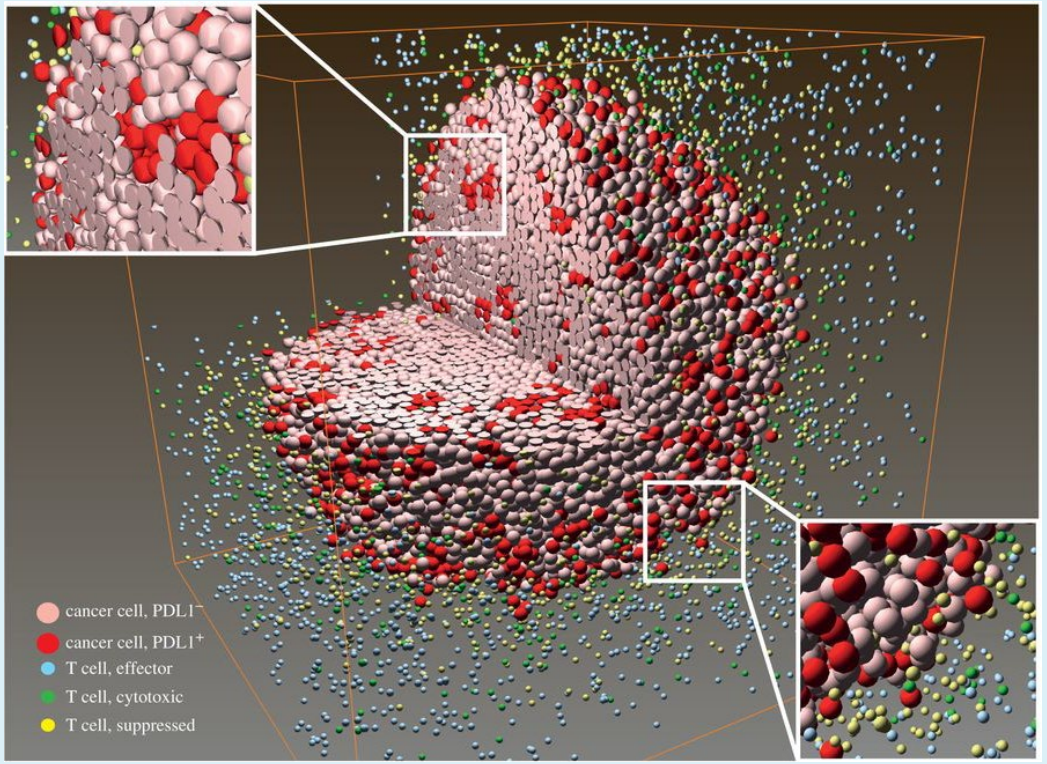
FROM MOLECULE TO PATIENT



Multi-scale Modeling in Clinical Oncology: Opportunities and Barriers to Success. Yankeelov TE, An G, Saut O, Luebeck EG, Popel AS, Ribba B, Vicini P, Zhou X, Weis JA, Ye K, Genin GM. Ann Biomed Eng. 2016 Sep;44(9):2626-41.

Agent-Based Model for Immuno-oncology





A computational multiscale agent-based model for simulating spatio-temporal tumour immune response to PD1 and PDL1 inhibition. Gong C, Milberg O, Wang B, Vicini P, Narwal R, Roskos L, Popel AS. J R Soc Interface. 2017 Sep;14(134).

Areas of Application

Getting Innovative Therapies Faster to Patients at the Right Dose: Impact of Quantitative Pharmacology Towards First Registration and Expanding Therapeutic Use

Satyaprakash Nayak[1], Oliver Sander[2], Nidal Al-Huniti[3], Dinesh de Alwis[4], Anne Chain[5], Marylore Chenel[6], Soujanya Sunkaraneni[7], Shruti Agrawal[7], Neeraj Gupta[8] and Sandra A.G. Visser[9]

FROM MOLECULE TO PATIENT

Dose

Biomarkers

Trial Design

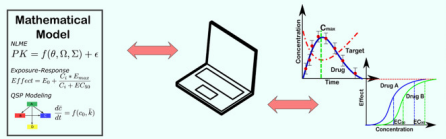
Combinations

Registration

Foundational Clinical Pharmacology Understanding of Asset

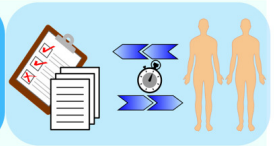
Integrated Team Effort in Drug Development Strategy

Recognized and Accepted by Decision Makers

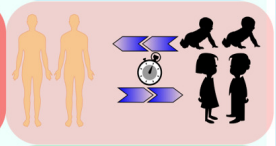


Model-Informed Knowledge Generation

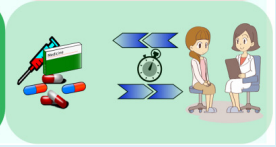
Rational Dose Selection for Pivotal Registration Trials



Reducing Trial Burden for Vulnerable Populations



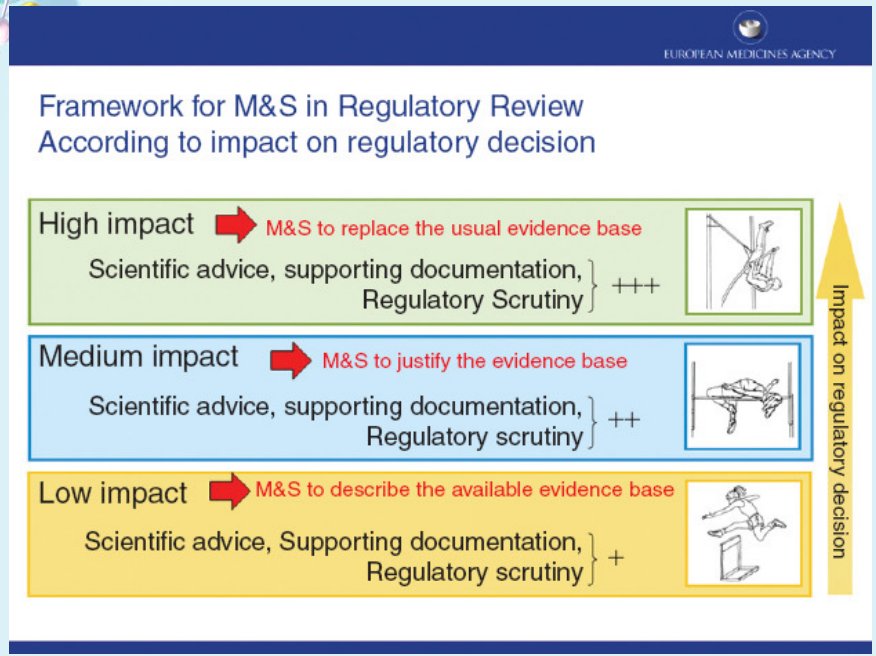
Simplified Dosing for Patients and Healthcare Providers



Getting Innovative Therapies Faster to Patients at the Right Dose: Impact of Quantitative Pharmacology Towards First Registration and Expanding Therapeutic Use. Nayak S, Sander O, Al-Huniti N, de Alwis D, Chain A, Chenel M, Sunkaraneni S, Agrawal S, Gupta N, Visser SAG. Clin Pharmacol Ther. 2018 Mar;103(3):378-383.

Despite Their Breadth, M&S Activities Are Underreported in Regulatory Submissions

FROM MOLECULE TO PATIENT



- Communication gap regarding M&S, both within industry and between industry and regulators
- Technical challenges, e.g. around standardization
- Data availability both within programs and among different programs and institutions
- Variable readiness by regulators or senior executives to evaluate M&S
- Influence of M&S expertise across discovery and development
- Suitability of the current eCTD format for including M&S results

The Role of Modeling and Simulation in Development and Registration of Medicinal Products: Output From the EFPIA/EMA Modeling and Simulation Workshop. Manolis E, Rohou S, Hemmings R, Salmonson T, Karlsson M, Milligan PA. CPT Pharmacometrics Syst Pharmacol. 2013 Feb 27;2:e31

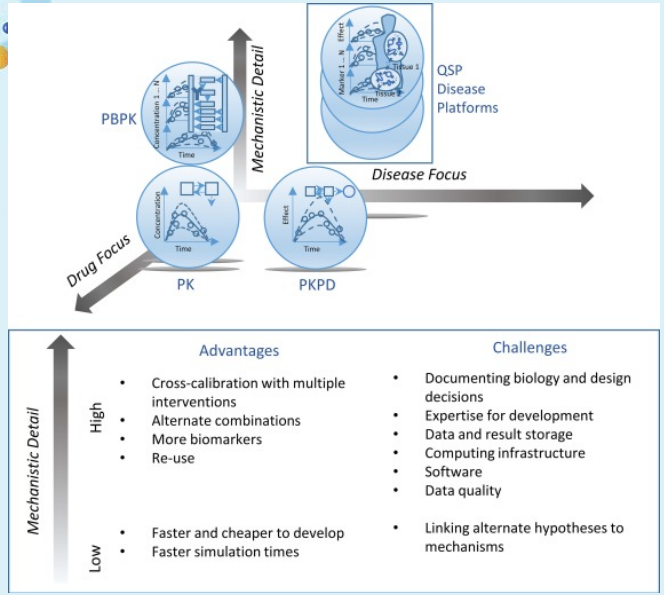
Case Study Compendium Is Important and Growing → QSP Platforms

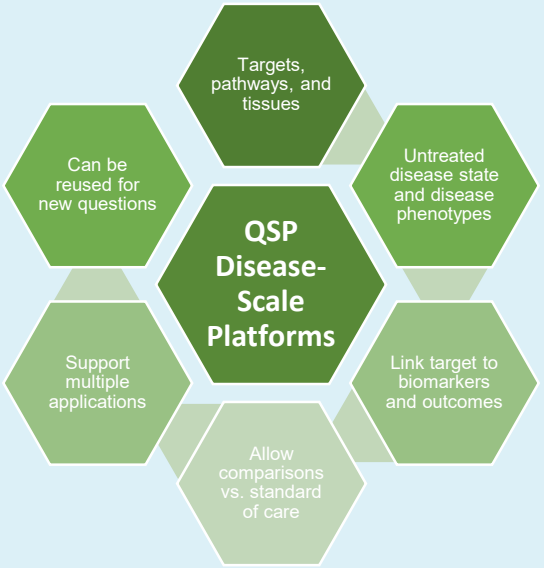
FROM MOLECULE TO PATIENT

Getting Innovative Therapies Faster to Patients at the Right Dose: Impact of Quantitative Pharmacology Towards First Registration and Expanding Therapeutic Use. Nayak S, Sander O, Al-Huniti N, de Alwis D, Chain A, Chenel M, Sunkaraneni S, Agrawal S, Gupta N, Visser SAG. Clin Pharmacol Ther. 2018 Mar;103(3):378-383.

The Discussion Around the Platform is as Important as the Platform Itself

FROM MOLECULE TO PATIENT

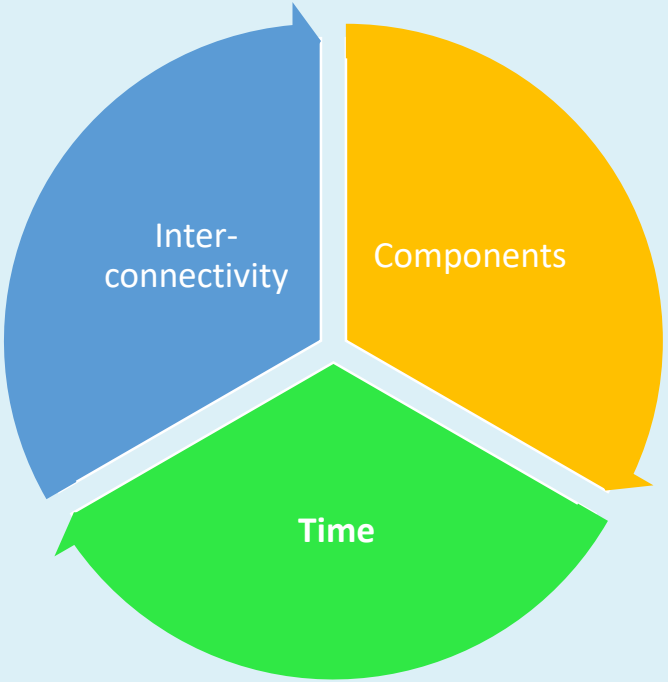




It can be difficult to make the case for return on investment for systems pharmacology platforms, but what about the data integration and communication they foster among project teams?

Quantitative Systems Pharmacology: A Case for Disease Models. Musante CJ, Ramanujan S, Schmidt BJ, Ghobrial OG, Lu J, Heatherington AC. Clin Pharmacol Ther. 2017 Jan;101(1):24-27.

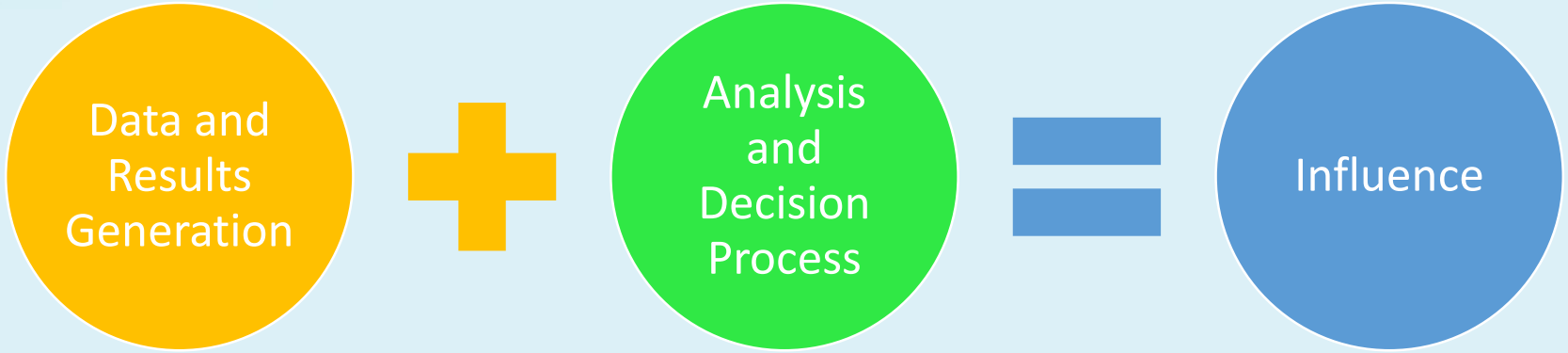
Success is a journey, not a destination. “The doing is often more important than the outcome”



Quote attributed to Arthur Ashe

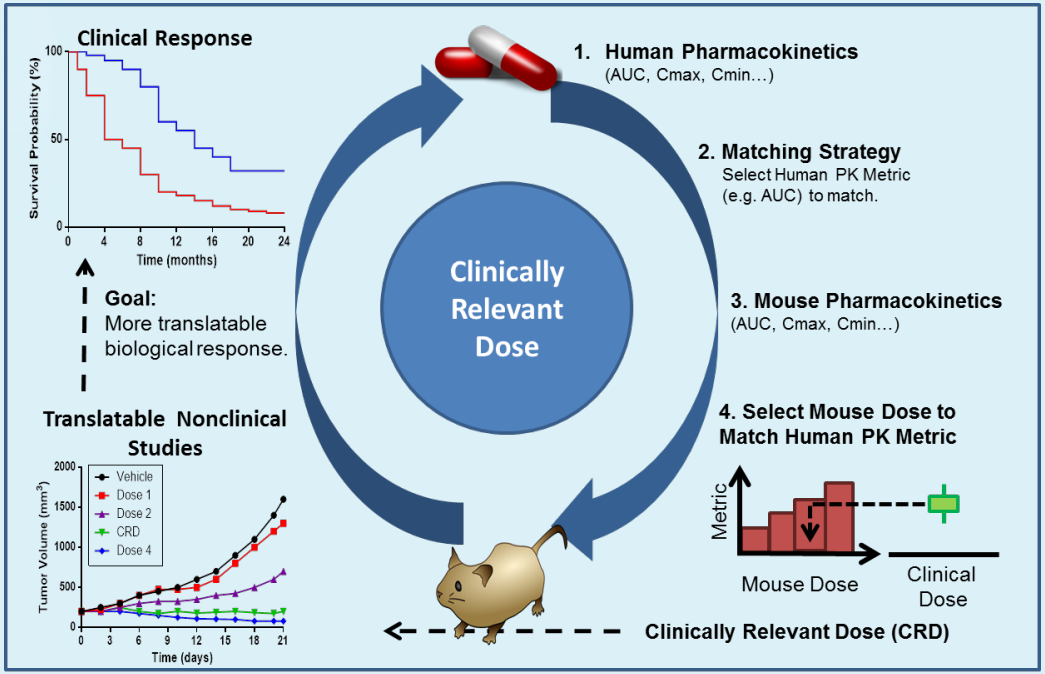
The promises of quantitative systems pharmacology modelling for drug development. V.R. Knight-Schrijver, V. Chelliah, L. Cucurull-Sanchez, N. Le Novère. Comput Struct Biotechnol J. 2016; 14: 363–370.

There Are Many Pathways to Influence



Quantitative Approaches to Improve Translational Studies

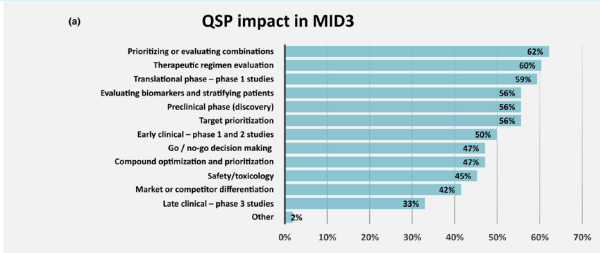
FROM MOLECULE TO PATIENT

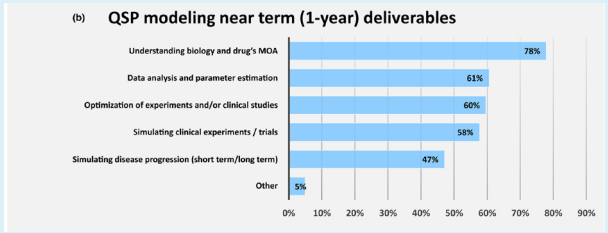


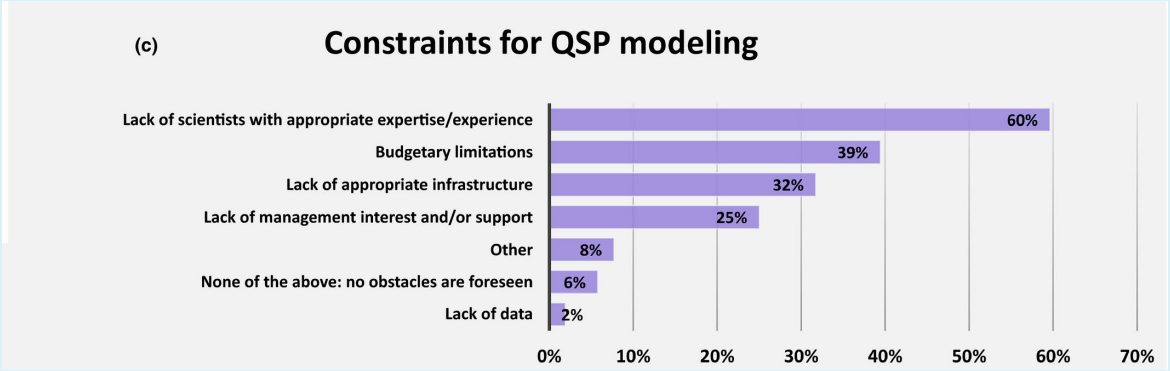
Found in Translation: Maximizing the Clinical Relevance of Nonclinical Oncology Studies. Spilker ME, Chen X, Visswanathan R, Vage C, Yamazaki S, Li G, Lucas J, Bradshaw-Pierce EL, Vicini P. Clin Cancer Res. 2017 Feb 15;23(4):1080-1090.

It's Not All About the Technology, but ROI for Other Benefits of QSP is Elusive

FROM MOLECULE TO PATIENT







The "constraints" listed are specific to the technical implementation of QSP principles and models

A Survey of Software Tool Utilization and Capabilities for Quantitative Systems Pharmacology: What We Have and What We Need. Sergey Ermakov Brian J. Schmidt Cynthia J. Musante Craig J. Thalhauser. CPT Pharmacometrics Syst Pharmacol. White Paper. First published: 12 November 2018.

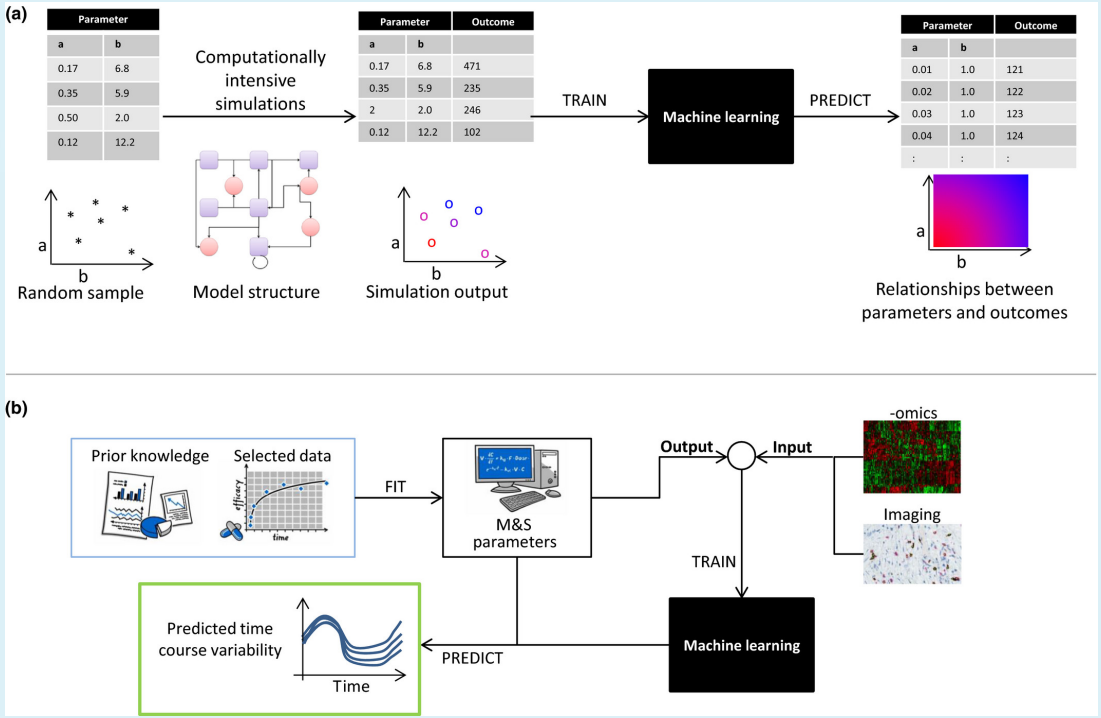
Roles for Machine Learning?

FROM MOLECULE TO PATIENT

At ASCPT 2019: How Artificial Intelligence and Machine Learning Are Revolutionizing Drug Discovery and Development, Thursday March 14 (available on ASCPT On Demand)

Image Credit: National Institutes of Health, BRAIN Initiative research program. BRAIN stands for Brain Research through Advancing Innovative Neurotechnologies. Learn more: www.braininitiative.nih.gov/

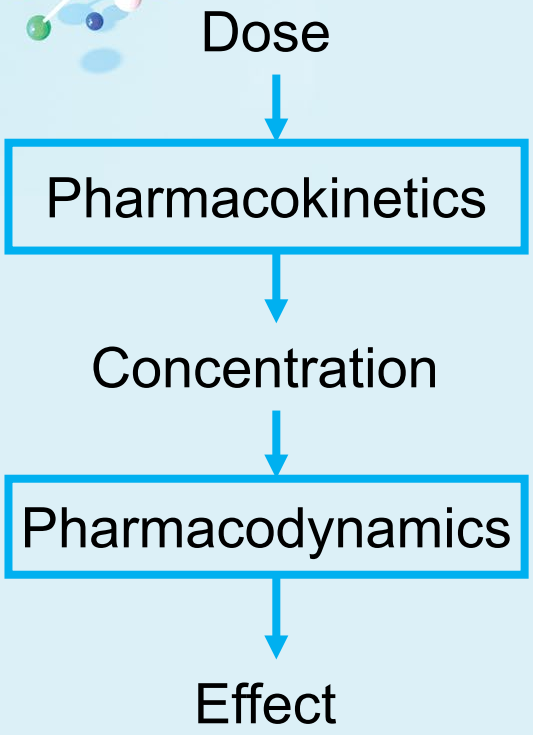
Machine Learning Can Support Existing M&S Paradigms



Models and Machines: How Deep Learning Will Take Clinical Pharmacology to the Next Level. Hutchinson L, Steiert B, Soubret A, Wagg J, Phipps A, Peck R, Charoin JE, Ribba B. CPT Pharmacometrics Syst Pharmacol. 2018 Dec 14.

Forward Looking Statements: How Does the Machine Learn? And Can It Help Us?

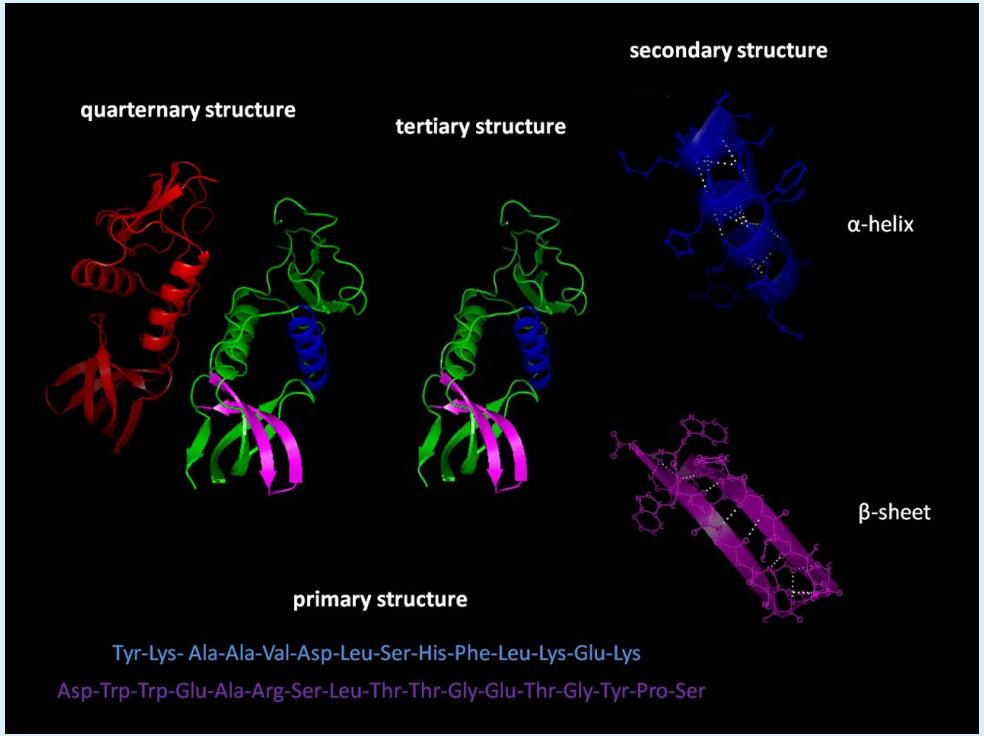
FROM MOLECULE TO PATIENT



- **Machine learning, neural networks**
  - "Linear" approximation of nonlinear functions
  - Works very well in many circumstances
- **PK-PD, QSP and PMX quantitative modelling**
  - Nonlinear approximations, based on mechanistic understanding, of highly nonlinear processes (functions)
- Can we back-calculate how the machine learns, so that it can help us in our mechanistic understanding?
- On the other hand, this may not be that useful since machines and humans learn differently

Recent Success of Machine Learning in 3D Protein Folding – CASP13

FROM MOLECULE TO PATIENT



Results of protein folding
https://en.wikipedia.org/wiki/Protein_folding#/media/File:Protein_structure.png

Strategies To Effectively Deploy Quantitative Systems Pharmacology Approaches In Clinical Development

FROM MOLECULE TO PATIENT

Influence

- Actual model deliverable and required predictions
- Thought process used for model development
- Influence on data collection and analysis
- Continue to apply QSP prospectively in development

Technology

- State of the art technology for model building
- Novel data sources and need for curation
- Incorporate emerging model building approaches
- Increase applications of QSP and pre-competitive sharing