Universiteit Leiden

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Quantitative Systems Pharmacology for Drug Discovery and Development

Piet van der Graaf

PMDA public seminar on "Frontline 0f utilization of modelling and simulation in disease research and therapeutic development

Tokyo, 3rd September 2019

What is Quantitative Systems Pharmacology (QSP)?

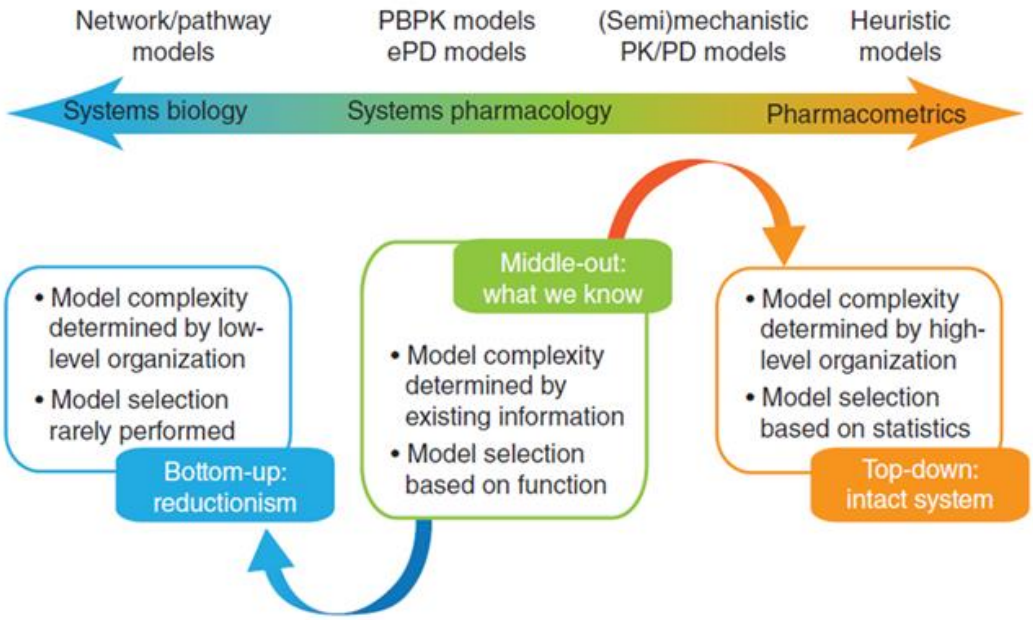
Pharm Res (2011) 28:1460–1464
DOI 10.1007/s11095-011-0467-9

PERSPECTIVE

Systems Pharmacology: Bridging Systems Biology and Pharmacokinetics-Pharmacodynamics (PKPD) in Drug Discovery and Development

Piet H. van der Graaf • Neil Benson

A recent development in this area is based on the growing realisation that innovation could be dramatically catalysed by creating synergy at the interface between systems biology (15) and PKPD (7,11), two disciplines which until now have largely existed in 'parallel universes' with a limited track record of impactful collaboration. This has led to the emergence of systems pharmacology (15). Broadly speaking, this is the quantitative analysis of the dynamic interactions between drug(s) and a biological system. In other words, systems pharmacology aims to understand the behaviour of the system as a whole, as opposed to the behaviour of its individual constituents; thus, it has become the interface between PKPD and systems biology. It applies the concepts of systems engineering, systems biology and PKPD to the study of complex biological systems through iteration between computational and/or mathematical modelling and experimentation



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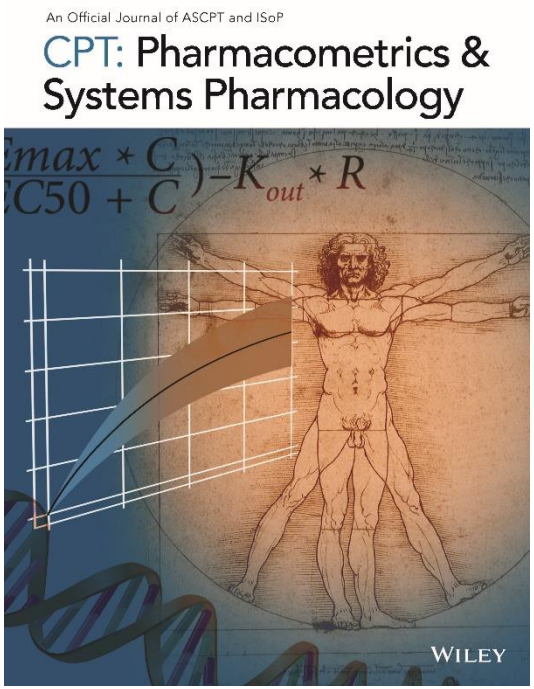
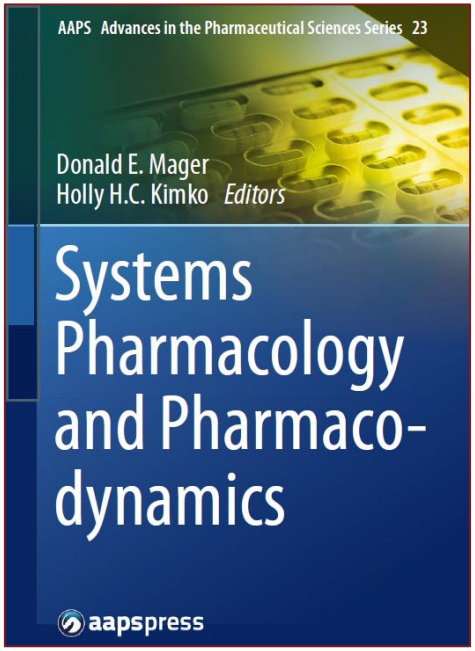
QSP: An established discipline

Journal



2012

Book



2016

Networks and Communities

ASCPT American Society for Clinical Pharmacology & Therapeutics

Member Services › Networks and Communities › Quantitative Pharmacology › S

Systems Pharmacology (SP) Community

aaps American Association of Pharmaceutical Scientists

SYSTEMS PHARMACOLOGY COMMUNITY

ISoP Special Interest Group

QSP

Quantitative Systems Pharmacology

UK Quantitative Systems Pharmacology NETWORK

IQ INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

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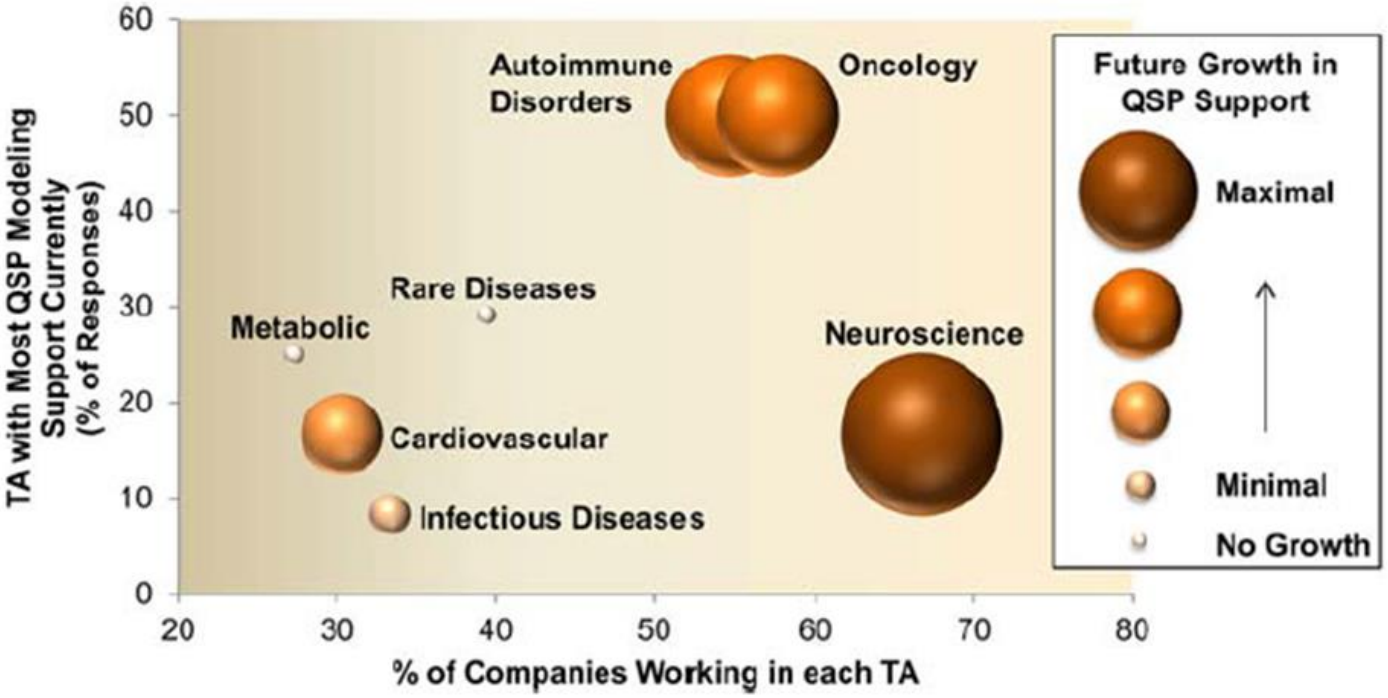
QSP uptake by Pharma

Citation: CPT Pharmacometrics Syst. Pharmacol. (2018) 00, 00; doi:10.1002/psp4.12282

REVIEW

Preclinical QSP Modeling in the Pharmaceutical Industry: An IQ Consortium Survey Examining the Current Landscape

Marjoleen J.M.A. Nijsen[1]*, Fan Wu[2], Loveleena Bansal[3], Erica Bradshaw-Pierce[4], Jason R. Chan[5], Bianca M. Liederer[6], Jerome T. Mettetal[7], Patricia Schroeder[8], Edgar Schuck[9], Alice Tsai[10], Christine Xu[11], Anjaneya Chimalakonda[12], Kha Le[13], Mark Penney[14], Brian Topp[15], Akihiro Yamada[16] and Mary E. Spilker[17]*



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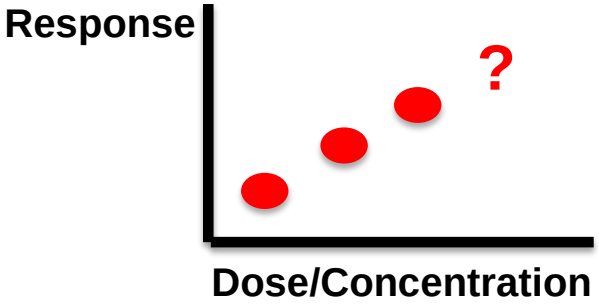
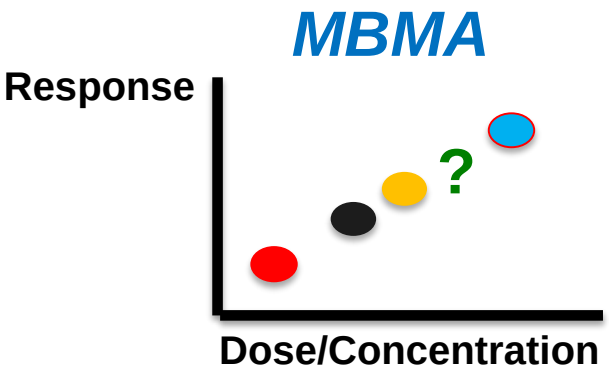
QSP: Extrapolation

Statistical Models

PMx

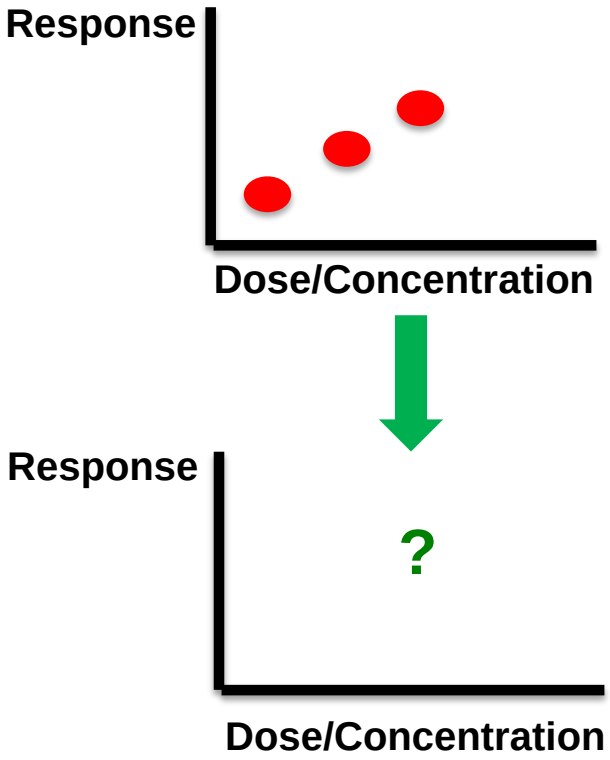


MBMA



Mechanistic Models

QSP



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Typical questions for QSP

- In a given biological pathway, what is the best target for pharmacological intervention to treat disease X?
- How can we improve the therapeutic effectiveness of an existing drug through combination therapy?
- Can we predict the effect of a drug in a special population?
- Can we individualise dosing regimen based on patient characteristics:
  - Which biomarkers do we require to achieve this?
- Can we predict human response to a novel mechanism based on preclinical data?:
  - What is the predicted human dose?
  - What is the best compound/modality?

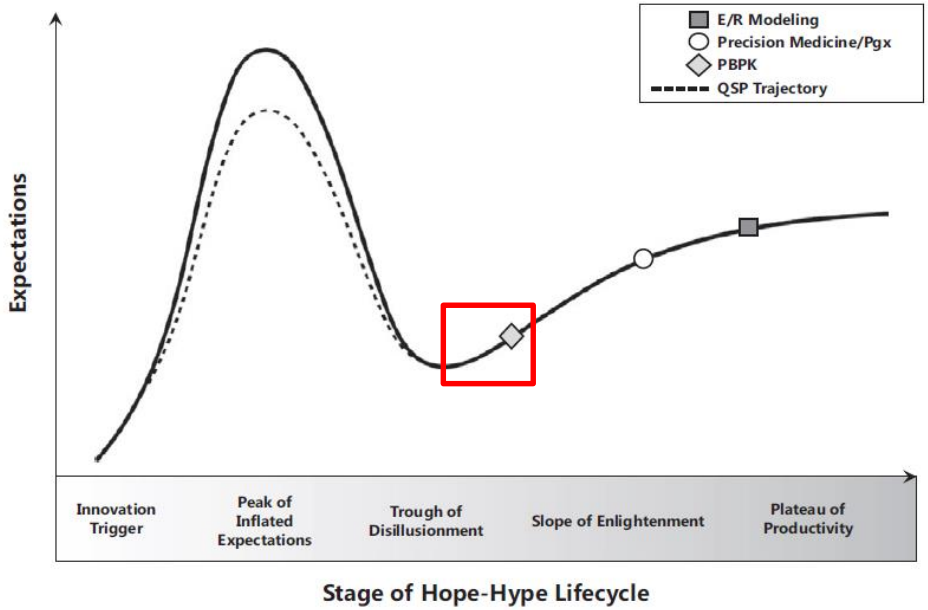
QSP uptake by Regulators

Citation: CPT Pharmacometrics Syst. Pharmacol. (2019) XX, 1–4; doi:10.1002/psp4.12403

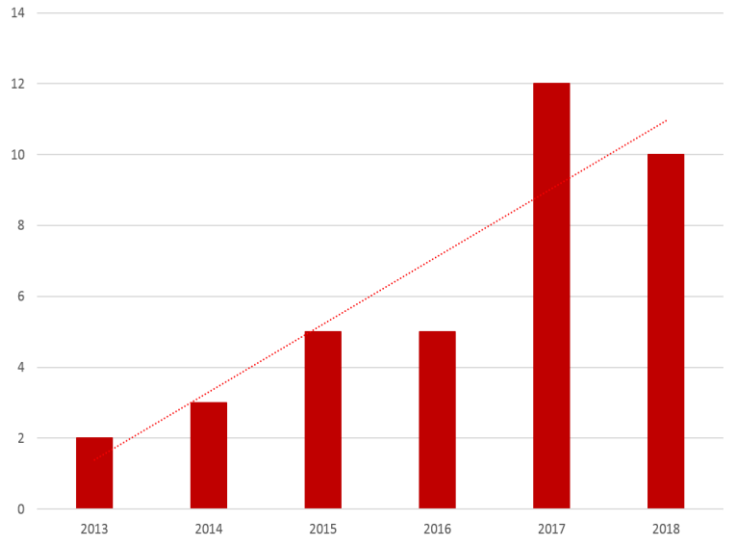
PERSPECTIVE

Quantitative Systems Pharmacology: A Regulatory Perspective on Translation

Issam Zineh[1,*]



FDA QSP submissions



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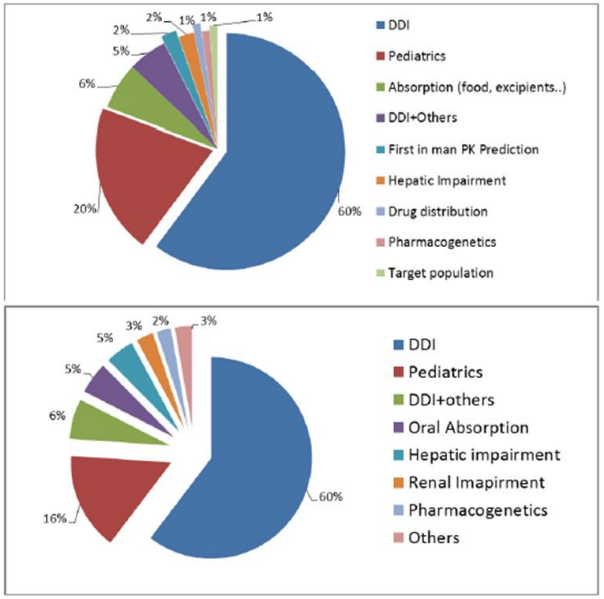
Still some way to go: comparison with PBPK

FDA submissions using PBPK modelling



Cumulative as of June 18, 2014 (n=96)

Sinha, MHRA PBPK Workshop 2014, London, UK

Cumulative as of Aug 1, 2016 (n=217)

Majority related to drug-drug interactions (DDIs, ~ 60%); pediatrics ranks the second

Ping Zhao

QSP: Dose (regimen) prediction and Target validation?

41 Labels with *in-silico* substitutes for clinical data informed by Simcyp

Pfizer Revatio (Sildenafil) Pulmonary Arterial Hypertension	**Johnson & Johnson** Xarelto (Rivaroxaban) Deep Vein Thrombosis and Pulmonary Embolism	**Tibotec** Edurant (Rilpivirine) HIV infection	**Ariad** Iclusig (Ponatinib) Chronic Myeloid Leukemia	**GW Pharma** Epidiolex (Cannabidiol) Epilepsy	**Lilly** Olumiant (Baricitinib) Rheumatoid Arthritis
Novartis Odomzo (Sonidegib) Basal Cell Carcinoma	**Janssen** Olysio (Simeprevir) Hepatitis C	**Actelion** Opsumit (Macitentan) Pulmonary Arterial Hypertension	**Pharmacyclics** Imbruvica (Ibrutinib) Mantle Cell Lymphoma and Chronic Lymphocytic Leukemia	**AstraZeneca** Movantik (Naloxegol) Opioid Induced Constipation	**Genentech** Cotellic (Cobimetinib) Metastatic Melanoma
Genzyme Cerdelga (Eliglustat) Gaucher Disease	**Sanofi** Jevtana (Cabazitaxel) Prostate Cancer	**Novartis** Zykadia (Ceritinib) Metastatic Non-small Cell Lung Cancer	**Pfizer** Bosulif (Bosutinib) Chronic Myelogenous Leukemia	**Alkermes** Aristada (Aripiprazole lauroxil) Schizophrenia	**AstraZeneca** Lynparza (Olaparib) Advanced Ovarian Cancer
Novartis Farydak (Panobinostat) Multiple myeloma	**Eisai** Lenvima (Lenvatinib) Thyroid cancer	**Genentech** Alecensa (Alectinib) Non-small Cell Lung Cancer	**AstraZeneca** Tagrisso (Osimertinib) Metastatic NSCLC	**Amgen** Blincyto (Blinatumomab) Acute Lymphoblastic Leukemia	**AstraZeneca** Calquence (Acalabrutinib) Mantle Cell Lymphoma
Eli Lilly Verzenio (Abemaciclib) Metastatic Breast Cancer	**Intercept** Ocaliva (Obeticholic acid) Primary Biliary Cholangitis	**Actelion** Uptravi (Selexipeg) Pulmonary Arterial Hypertension	**Janssen** Invokana (Canagliflozin) Type 2 Diabetes	**Merck** Prevymis (Letermovir) Cytomegalovirus	**Merck** Steglujan (Ertugliflozin) Type 2 Diabetes
Novartis Kisqali (Ribociclib succinate) Metastatic Breast Cancer	**PTC Therapeutics** Emflaza (Deflazacort) Duchenne Muscular Dystrophy	**Shionogi** Symproic (Naldemedine) Opioid Induced Constipation	**Spectrum** Beleodaq (Belinostat) Peripheral T-cell Lymphoma	**UCB** Briviact (Brivaracetam) Epilepsy	**Vertex** Symdeko (Tezacaftor/ivacaftor) Cystic Fibrosis
Novartis Rydapt (Midostaurin) Acute Myeloid Leukemia	**Ariad** Alunbrig (Brigatinib) Metastatic Non-small Cell Lung Cancer	**Janssen** Erleada (Apalutamide) Non-metastatic Prostate Cancer	**Helsinn** Akynzeo (fosnetupitant/palonosetron) Acute and Delayed Nausea	**AkaRx** Doptelet (Avatrombopag maleate) Thrombocytopenia	

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Application of QSP in Regulatory Review: FDA

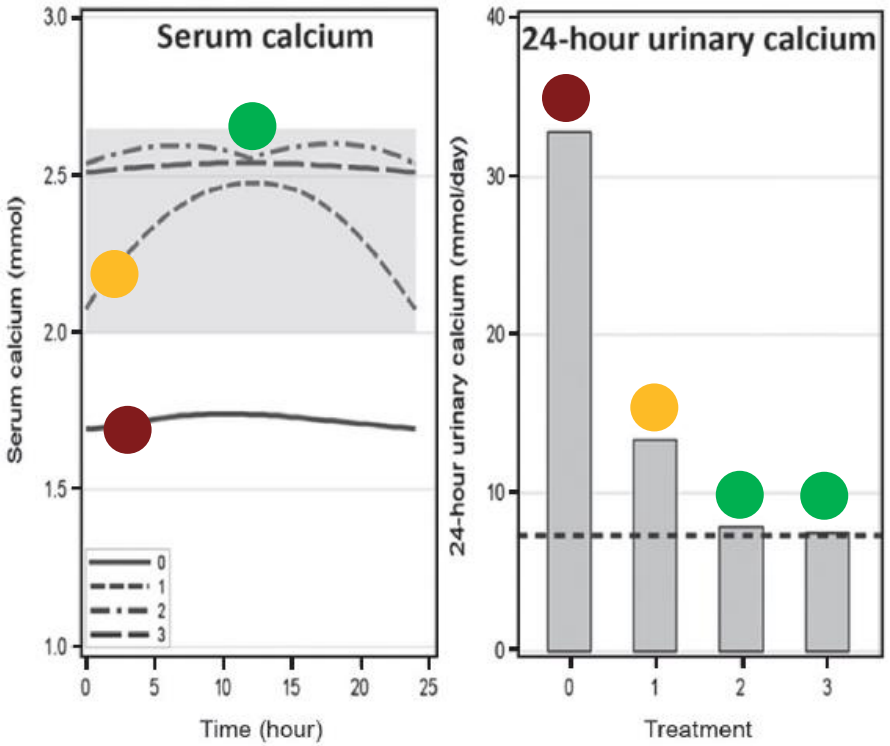
CLINICAL PHARMACOLOGY & THERAPEUTICS

doi:10.1002/cpt.1200

Use of a Systems Pharmacology Model Based Approach Toward Dose Optimization of Parathyroid Hormone Therapy in Hypoparathyroidism

Manoj Khurana[1], Immo Zadezensky[2,*], Naomi Lowy[3], Dragos Roman[3], Jean-Marc Guettier[4,*], Liang Li[1], Jeffry Florian[3], Chandrahas G. Sahajwalla[1], Vikram Sinha[5,*] and Nitin Mehrotra[5,*]

- Placebo
- Proposed regimen
- QSP suggested regimen



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Application of QSP in Regulatory Review: EMA

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 104 NUMBER 5 | NOVEMBER 2018

The Role of Quantitative Systems Pharmacology in the Design of First-in-Human Trials

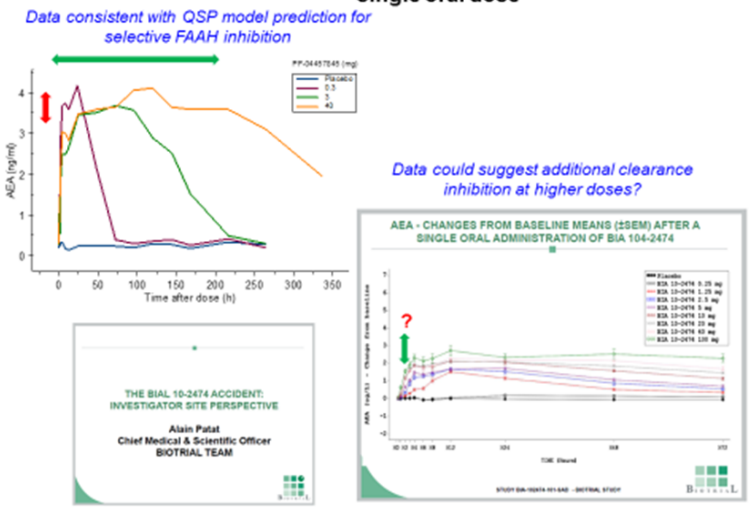
Piet H. van der Graaf[1,2] and Neil Benson[2]

ORIGINAL ARTICLE

A Systems Pharmacology Perspective on the Clinical Development of Fatty Acid Amide Hydrolase Inhibitors for Pain

N Benson[1], E Metelkin[2], O Demin[2], GL Li[3], D Nichols[4] and PH van der Graaf[5]

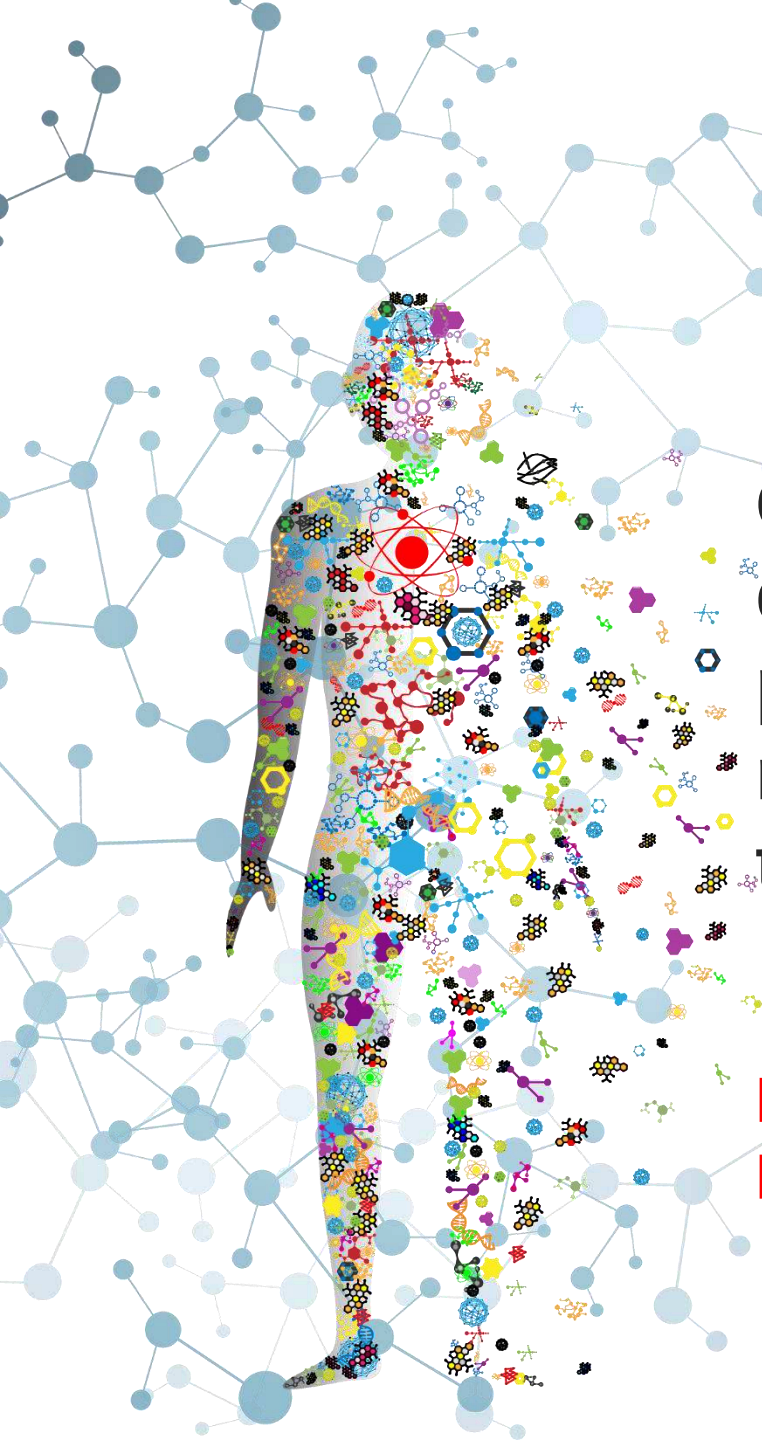
Elevation of AEA observed in healthy volunteers following a single oral dose



Response to: "The Role of Quantitative Systems Pharmacology in the Design of First-in-Human Trials"

Kevin Blake[1], Milton Bonelli[1], Stefano Ponzano[1], Harald Enzmann[2], on behalf of the European Medicines Agency Committee for Human Medicinal Products "First-in-Human Guideline Drafting Group"[†]

EMA encourages the development and use of complementary mechanistic models in translational drug research, such as the present example. Guidance on novel technologies can be obtained from EMA under the form of a qualification advice or a qualification opinion (Qualification of novel methodologies for medicine development: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&mid=WC0b01ac0580022bb0. Accessed 8 June 2018). Their inclusion in future guidelines will be further considered in line with increasing scientific knowledge.

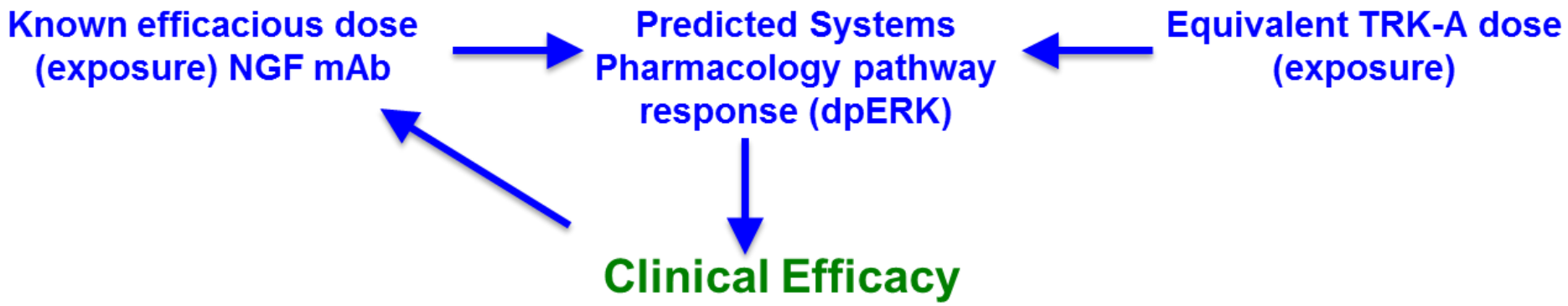


Clinical validation of a quantitative systems pharmacology (QSP) model for nerve growth factor (NGF) pain therapies

Piet van der Graaf, Tomomi Matsuura, Mike Walker & Neil Benson

TrkA: target validation

V Biology	•TrkA (neurotrophic receptor tyrosine kinase 1) key node in NGF pathway
V Chemistry	•Kinases 'good' targets – viewed as druggable
? Pharmacology	•QSP model



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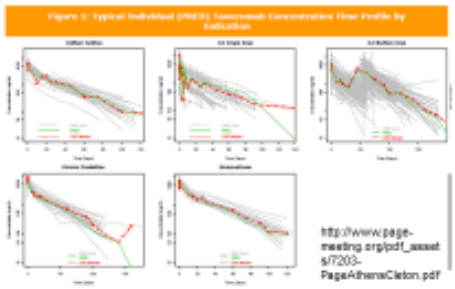
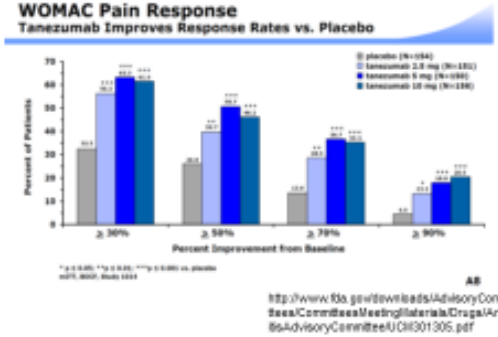
QSP model predictions

- **NGF mAb: ~1000 x K_D**

Model predictions quantitatively concordant with data for prototype NGF mAbs eg tanezumab

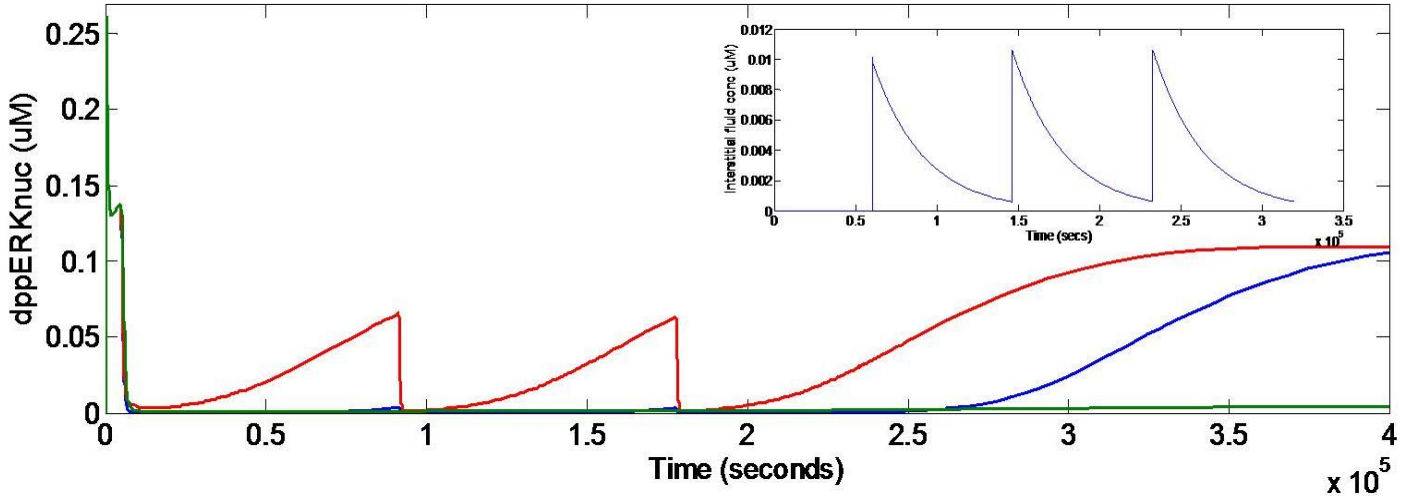
- **Model prediction consistent with clinical pain data**
- **Clinical optimal dose for efficacy reported ~ 5-10 mg**





- **TrkA small molecule: xx K_D**

⇒ Efficacy & dose could have been predicted from QSP model (before any clinical data were published)



Impact of a compound that binds NGF (green) versus TrkA kinase inhibitor with different pharmacological properties (red and blue) on the dppERK response

FIH confirms QSP predictions

British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2017) •• ••–•• 1

PHARMACODYNAMICS

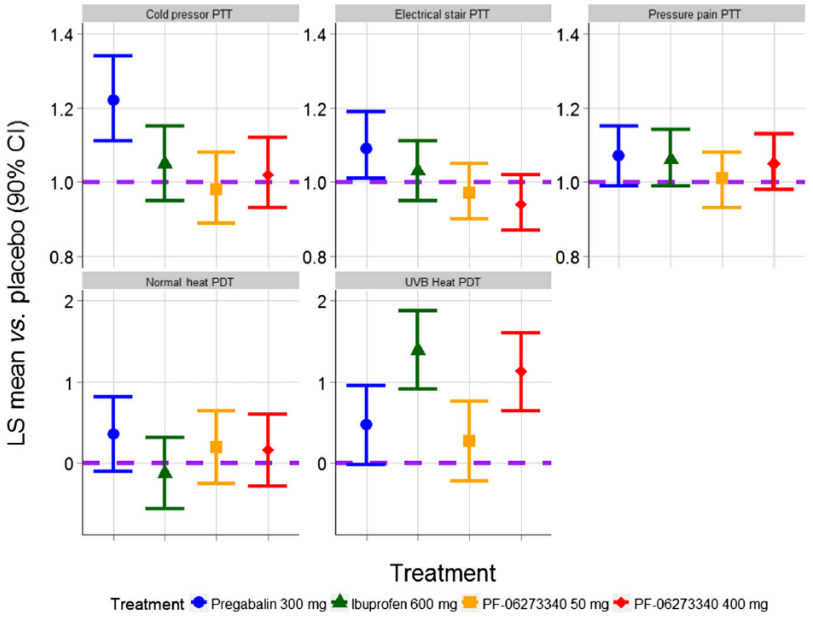
Demonstration of an anti-hyperalgesic effect of a novel pan-Trk inhibitor PF-06273340 in a battery of human evoked pain models

Correspondence Dr Donal Gorman, Neuroscience and Pain Research Unit, Pfizer WRD, Cambridge, UK. Tel.: +44 13 0464 1231; E-mail: donal.gorman@pfizer.com

Received 23 November 2016; **Revised** 30 August 2017; **Accepted** 23 September 2017

Peter Loudon[1], Pieter Siebenga[2], Donal Gorman[1], Katrina Gore[1], Pinky Dua[1], Guido van Amerongen[2], Justin L. Hay[2], Geert Jan Groeneveld[2] and Richard P. Butt[1]

[1]*Neuroscience and Pain Research Unit, Pfizer WRD, Cambridge, UK and* [2]*Centre for Human Drug Research, Zernikedreef 8,2333 CL Leiden, the Netherlands*



the lower dose achieved was ~ 4 × IC_{50} at C_{max} and dropped to ~1 × IC_{50} at 4 h. The differential efficacy of these two doses implies that, at least for this endpoint, an exposure that achieves a multiple of IC_{50} throughout the assessment period is required for an acute PD effect in inflammatory pain. This conclusion is consistent with the prediction from a systems pharmacology model of the NGF pathway [18] utilizing PF-06273340 data. Further studies are needed to determine

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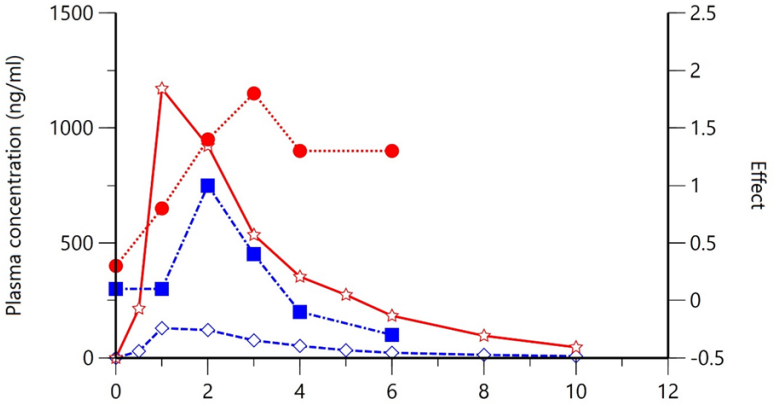
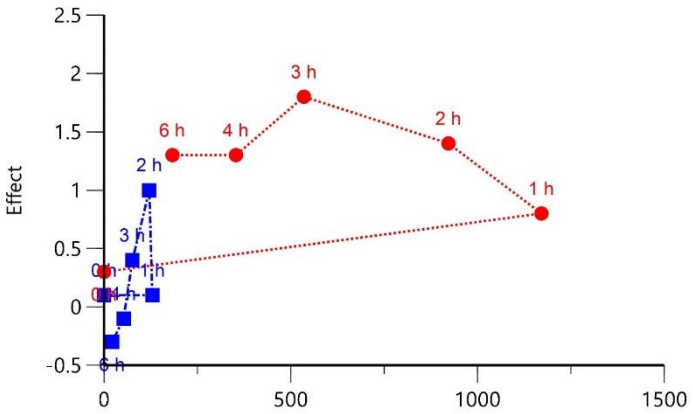
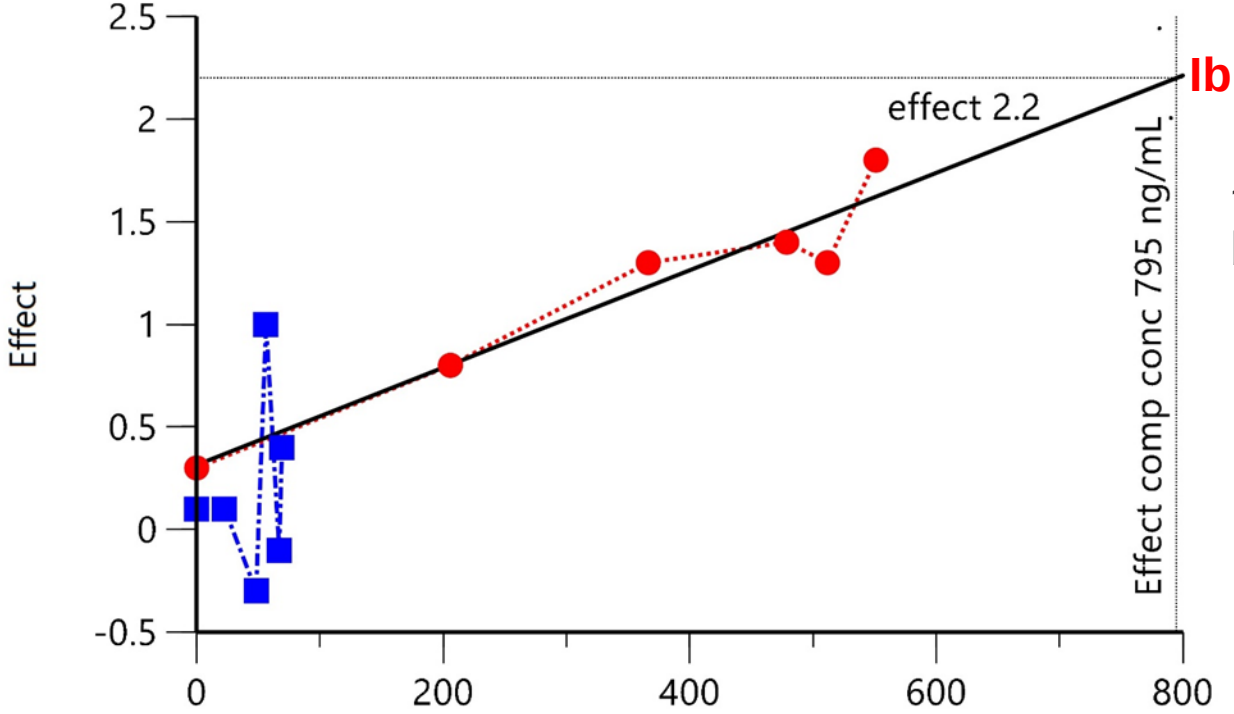
PKPD analysis reveals inferiority compared to SoC







Ibuprofen 600 mg

~275/20-fold IC_{50} bound/unbound

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Tanezumab proceeding to filing with a single low dose in OA only

12 August 2019

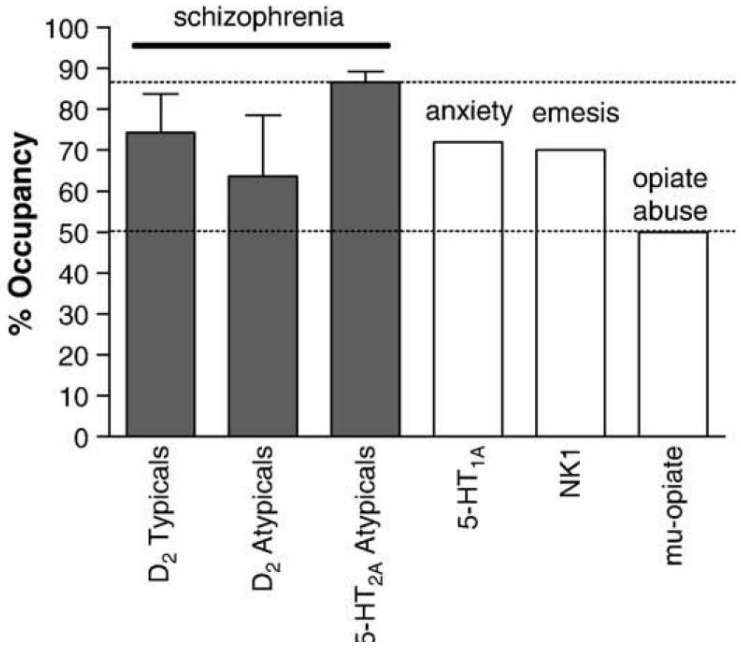
Estimated market value: anti-NGFs drug class

ANALGESIC INNOVATION

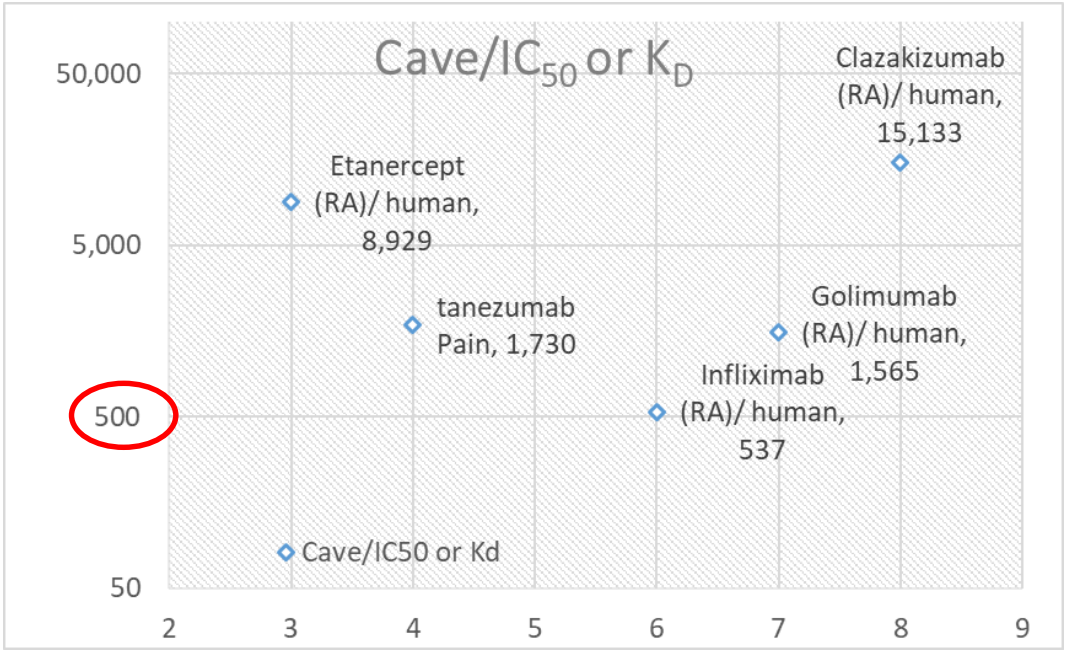
Efficacious concentration rule of thumb: ~3-10 x K_i ?

Target site occupancy: Emerging generalizations from clinical and preclinical studies ☆

Sarah Grimwood [a,*], Paul R. Hartig [b]



Anti-inflammatory/Pain mAbs



approximately 60–90% target occupancy is required for G protein-coupled receptors, neurotransmitter transporters, and ligand-gated ion channels. Effective doses of agonists occupy a wider range of their target

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QSP models as platforms

NGF QSP model:

- Continuous development since ~2010
- Utilized in >5 drug discovery/development programs:
  - Multiple targets
  - Multiple modalities
  - Combination therapies
- One of the first examples of QSP model reduction

NGF model reduction

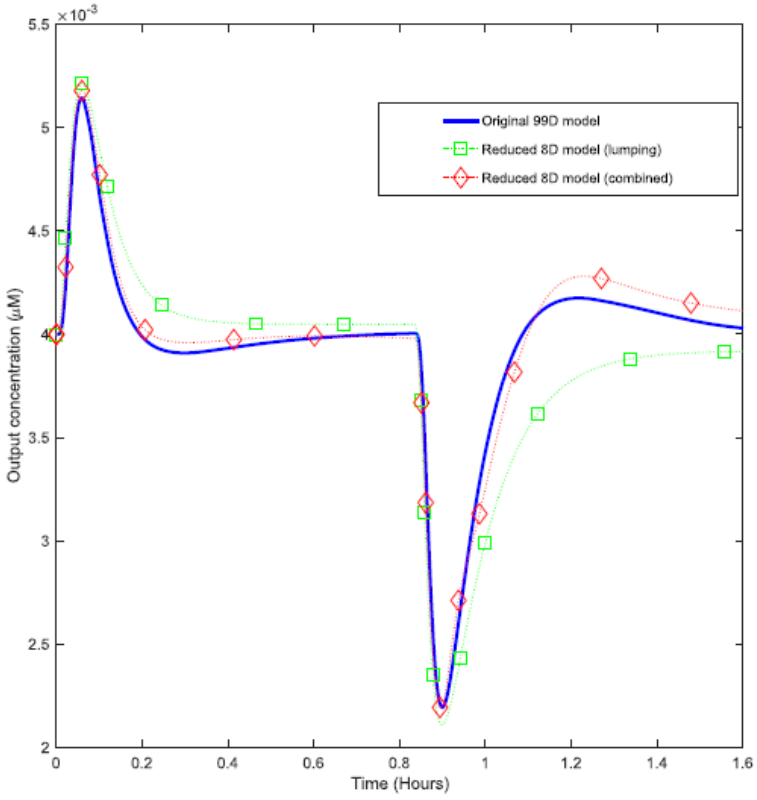
Snowden et al. BMC Systems Biology (2017) 11:17
DOI 10.1186/s12918-017-0397-1

BMC Systems Biology

METHODOLOGY ARTICLE Open Access

A combined model reduction algorithm for controlled biochemical systems

Thomas J. Snowden[1,2], Piet H. van der Graaf[3,2] and Marcus J. Tindall[1,4*]



Dimension	EBT error	Lumping error	Stiffness	Combined error
75	0.76%	≈ 0%*	42658	–
50	#	0.01%	42633	–
25	#	0.52%	10664	–
15	#	1.26%	7934	–
14	#	2.21%	7934	–
13	#	2.29%	7934	–
12	#	1.21%	1591	–
11	#	3.07%	236	–
10	#	6.02%	264	2.84%
9	#	10.96%	211	4.02%
8	#	13.12%	43	4.32%
7	#	14.18%	42	4.77%
6	#	29.53%	44	13.08%
5	#	39.03%	45	20.81%
4	#	46.47%	212	31.09%
3	#	54.67%	42	34.58%
2	#	53.52%	18	41.10%
1	#	55.73%	1	50.46%

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QSP Big Topics

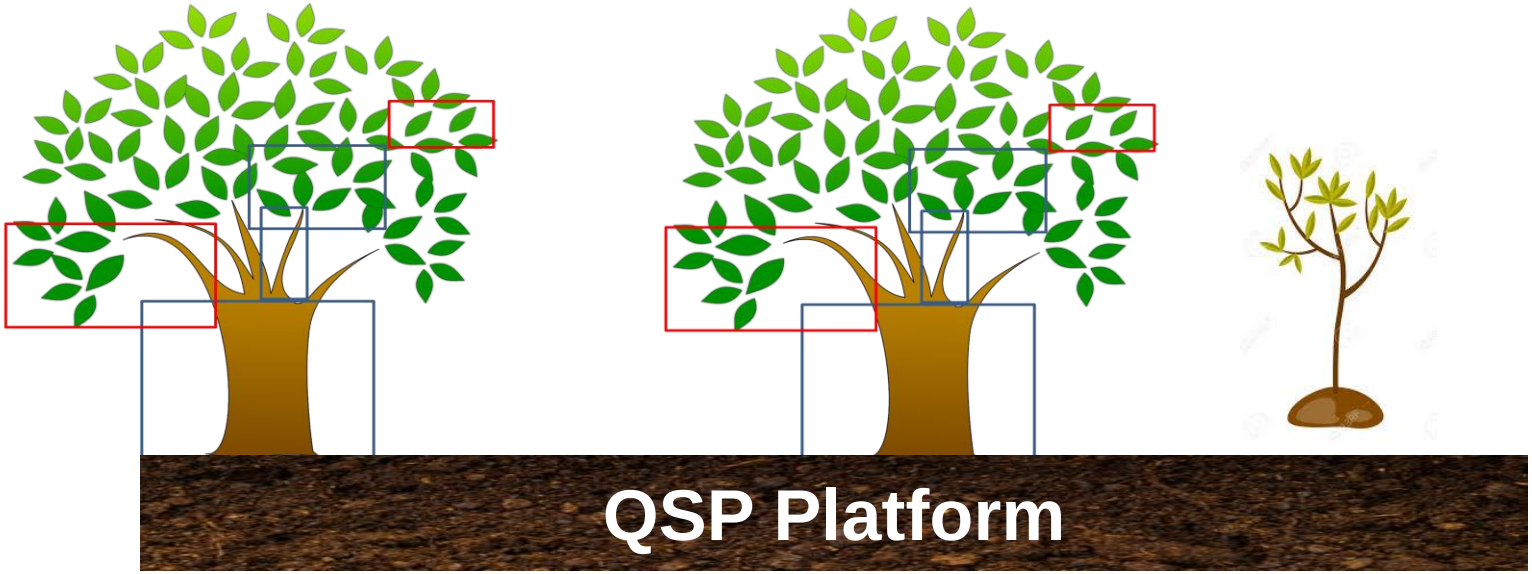
- Immunogenicity
  - Predict impact on PKPD for biologicals
  - Bio-similars
- Immuno-Oncology
  - Combination therapy: target selection and dosing schedule
- Neurodegenerative diseases
  - Target validation in Alzheimer's Disease
- Infectious Diseases
  - Resistance, vaccination
- ….

Certara QSP Consortia

Immuno-Oncology Consortium

Immunogenicity Consortium

Neurodegeneration Consortium



Each QSP Consortium is a tree, where trunk represents biology common to all applications, while branches and leaves represent target specific mechanisms. Consortia are rooted in QSP Platform.

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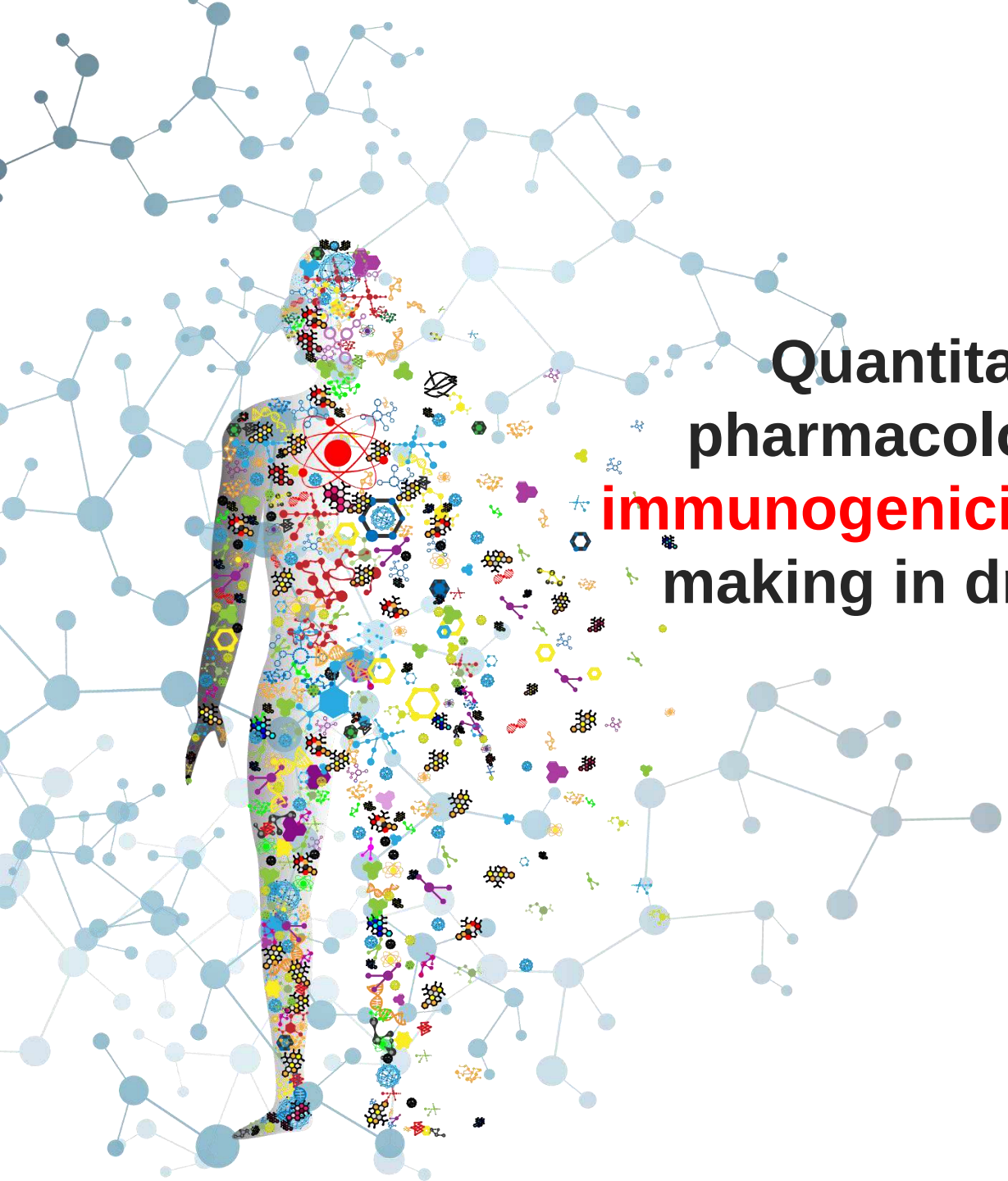

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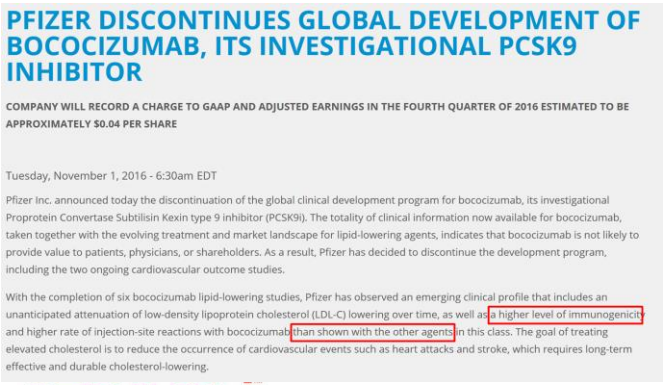
Quantitative systems pharmacology modeling of immunogenicity (IG) for decision making in drug development

Problem statement

- **Biologicals:**
  - ~30% of new drug approvals (12/46 FDA 2017)
  - $445 billion sales projected 2019

- **Immunogenicity (IG):**
  - 89% incidence; 49% efficacy impacted

→*Management of IG will be a significant and recurring topic in interactions between sponsors and regulatory agencies*



PFIZER DISCONTINUES GLOBAL DEVELOPMENT OF BOCOCIZUMAB, ITS INVESTIGATIONAL PCSK9 INHIBITOR

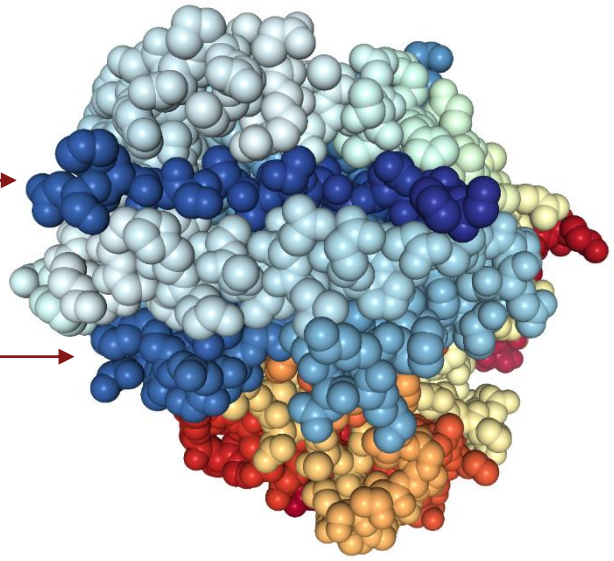
COMPANY WILL RECORD A CHARGE TO GAAP AND ADJUSTED EARNINGS IN THE FOURTH QUARTER OF 2016 ESTIMATED TO BE APPROXIMATELY $0.04 PER SHARE

Tuesday, November 1, 2016 - 6:30am EDT

Pfizer Inc. announced today the discontinuation of the global clinical development program for bococizumab, its investigational Proprotein Convertase Subtilisin Kexin type 9 inhibitor (PCSK9i). The totality of clinical information now available for bococizumab, taken together with the evolving treatment and market landscape for lipid-lowering agents, indicates that bococizumab is not likely to provide value to patients, physicians, or shareholders. As a result, Pfizer has decided to discontinue the development program, including the two ongoing cardiovascular outcome studies.

With the completion of six bococizumab lipid-lowering studies, Pfizer has observed an emerging clinical profile that includes an unanticipated attenuation of low-density lipoprotein cholesterol (LDL-C) lowering over time, as well as a higher level of immunogenicity and higher rate of injection-site reactions with bococizumab than shown with the other agents in this class. The goal of treating elevated cholesterol is to reduce the occurrence of cardiovascular events such as heart attacks and stroke, which requires long-term effective and durable cholesterol-lowering.

Case study: PCSK9



Genentech
A Member of the Roche Group

(Kapil Gadkar & Jennifer Rohrs)

Antibody Drug	# Binding peptides*	# MHC II alleles	% ADA+ Patients
Bococizumab (Pfizer)	2	12	68% (Ridker, 2017)
Alirocumab (Regeneron)	1	1	5.1% (Roth, 2017)
Evolocumab (Amgen)	0	0	0.1% (Henry, 2016)
GNE anti-PCSK9 (Genentech)	2	8	4% (GENE data*)

**Based on Phase II clinical study with ~200 subjects*

IG is mostly tackled preclinically:

- Bioinformatics prediction of peptides that bind strongly to major histocompatibility (MHC) II receptors;
- Protein engineering to avoid strong binding.

Limited power of bioinformatics approach to predict clinical outcome indicates that other factors than MHC II binding are important (e.g. co-therapy, disease, age).

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IG is highly variable

Table 3 Summary of ADAb formation rates for individual biologic/biosimilar by chronic inflammatory disease

Biologic	Frequency of ADAb formation, % (no. of studies[a])							
	RA	PsA	JIA	AS	Ps	CD	UC	Range
ABA	2–20 (7)		2–11 (2)					2–20 (9)
ADA	0–51 (33)	0–54 (8)	6–33 (6)	8–39 (9)	0–51 (12)	0–35 (13)	3–5 (3)	0–54 (80)
CZP	2.8–37 (7)				21 (1)	3–25 (6)		3–37 (14)
ETN	0–13 (25)	0 (3)	0–6 (2)	0 (4)	2–5 (5)			0–13 (37)
GLM	2–10 (11)	6 (1)		0–6.4 (2)			0–19 (8)	0–19 (22)
INF	8–62 (48)	15–33 (3)	26–42 (2)	6.1–69 (10)	0–41 (12)	3–83 (29)	6–46 (10)	0–83 (110)
RTX	0–21 (8)							0–21 (8)
SEC		0–0.1 (3)		0–0.3 (3)	0–1 (8)			0–1 (14)
TCZ	0–16 (14)		1–8 (3)					0–16 (17)
UST		8–11 (3)			4–8.6 (10)	0–1 (2)		1–11 (15)
CT-P13	26–52 (2)			27 (1)		21 (1)	24 (1)	21–52 (5)

- Compound
- **Dose and administration**
- Patient population
- **Disease state**
- Co-medication
- **Other**

A quantitative, predictive tool is required to manage IG in drug development and guide regulatory decision making: Simcyp's precedented approach in PBPK

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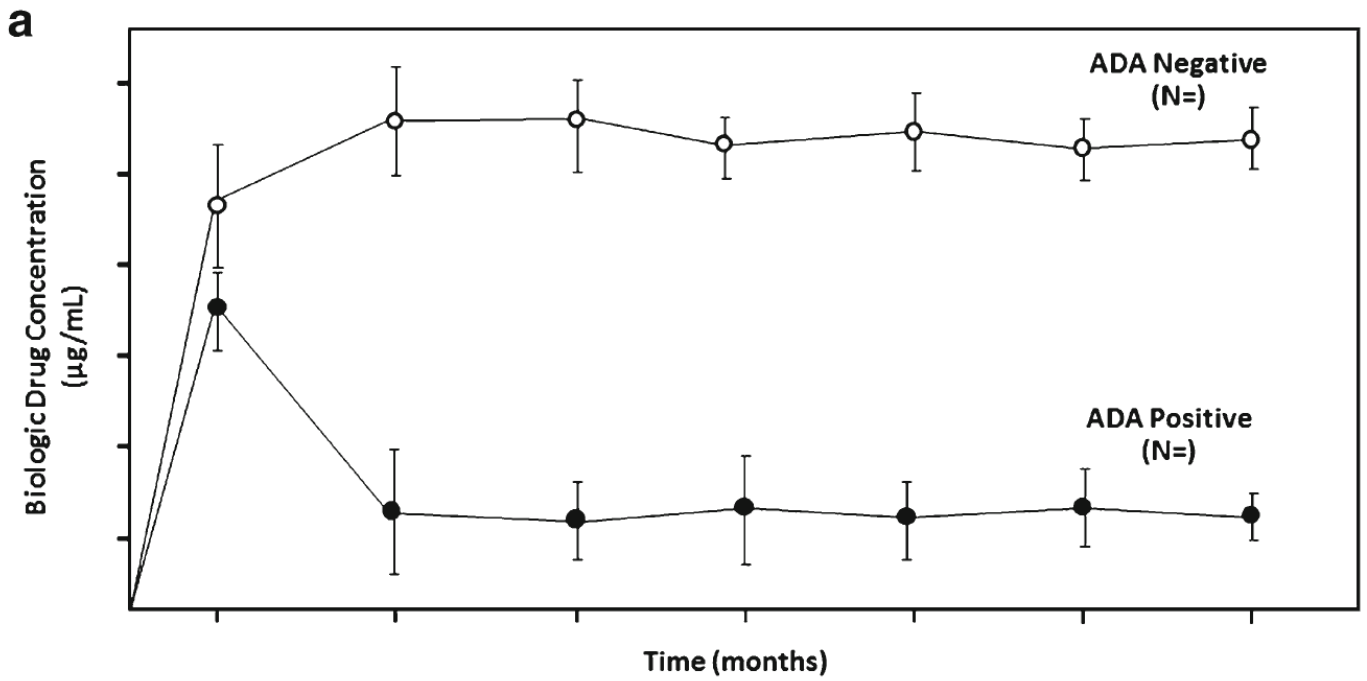
Impact on Pharmacokinetics (PK)



Shankar et al. Assessment and Reporting of the Clinical Immunogenicity of Therapeutic Proteins and Peptides—Harmonized Terminology and Tactical Recommendations. The AAPS Journal, Vol. 16, No. 4, July 2014 (Figure 3a).

*"ADA bind the biologic drug in circulation to form immune complexes which, (…), may be **cleared faster** from the body than unbound drug. Alternatively, for some products, the formation of immune complexes leads to recirculation and **prolonged half-life**. (…), these clearing or drug sustaining ADA responses can affect the PK profile such that drug clearance rates are increased or decreased respectively leading to altered drug exposure. **Thus, it is important to examine the effects of ADA response on PK.**"*

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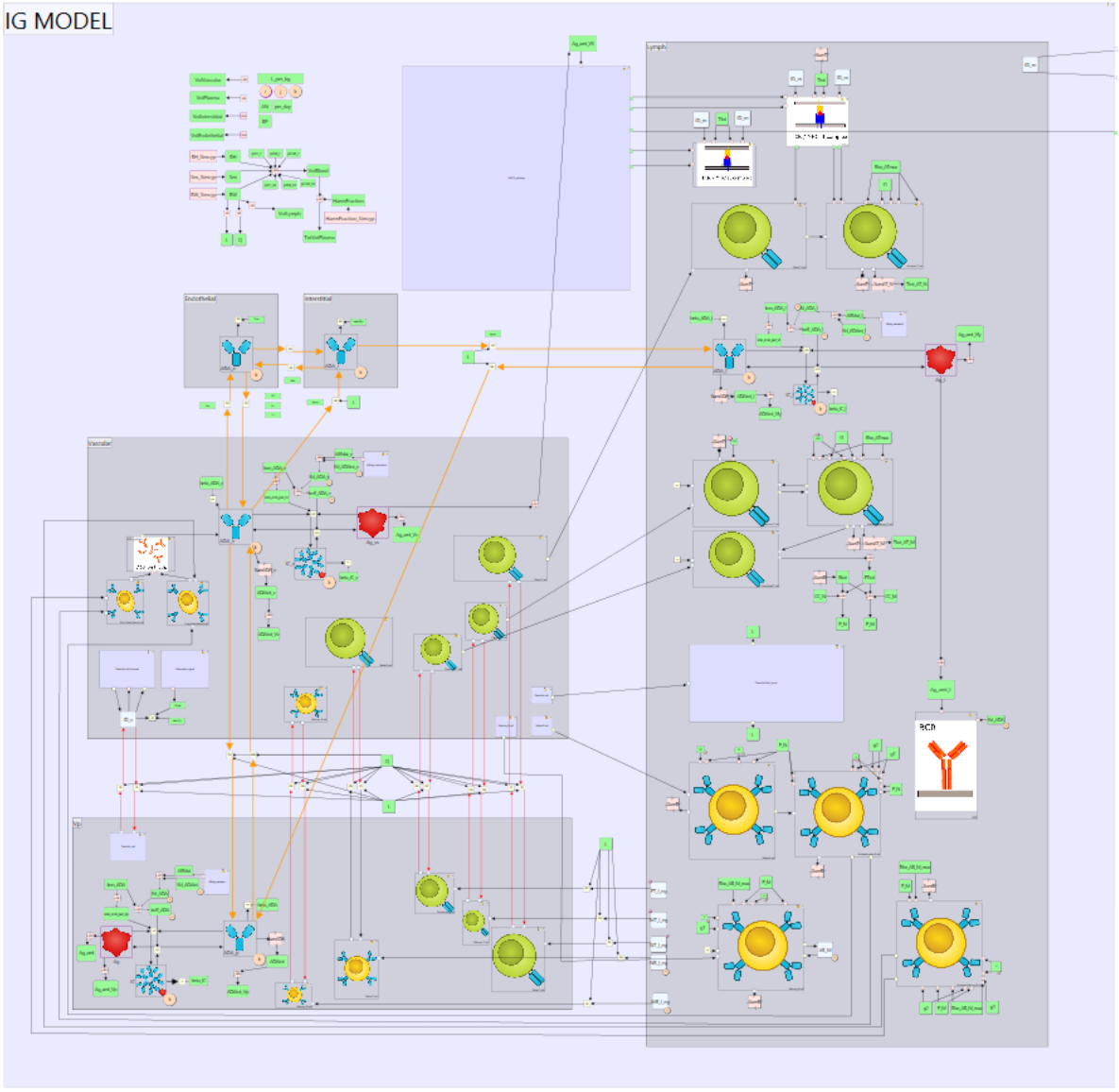
IG Model: Scope of biology



- Peripheral blood, vascular blood and lymph compartments.
- Immature and mature dendritic cells.
- Naïve, activated, memory, functional CD4 T-cells.
- Naïve, activated, memory, short lived plasma, long lived plasma B-cells.
- Leukocyte circulation with blood and lymph flows.
- Migration to lymph vessels, entry through high epithelial venules and egress to efferent lymph vessels.
- Protein digestion and peptide:MHCII binding.
- Antigen presentation and T-cell activation.
- B-cell activation.
- ADA synthesis and distribution.
- Affinity maturation.
- Immune complex formation.
- PBPK model for compound administration, distribution and elimination (not shown on map; Simcyp connection).

Version 8.0.3

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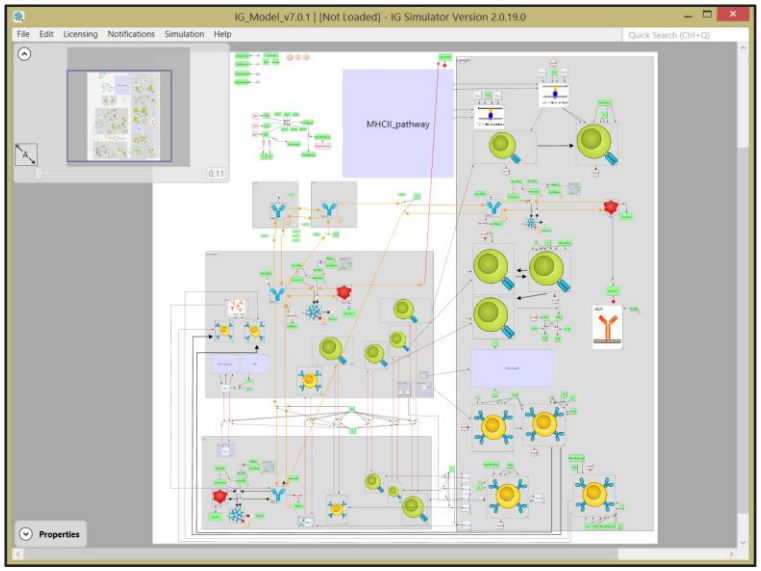
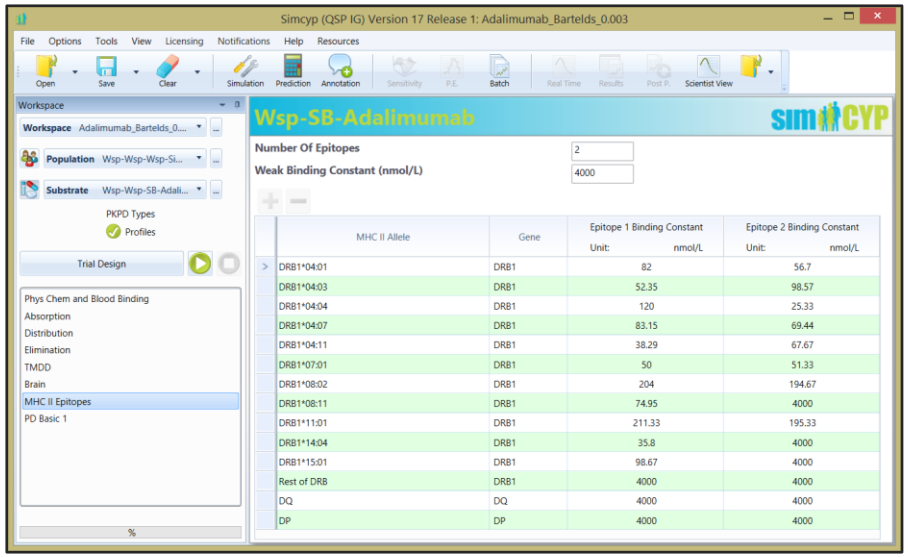
Overview of IG Simulator

Biological Process Map interface



Read workspace file.

Simcyp simulator



Export IG Model code.

Write IG Model

Read IG Model and augment ODEs

Simulate virtual trial and output results.

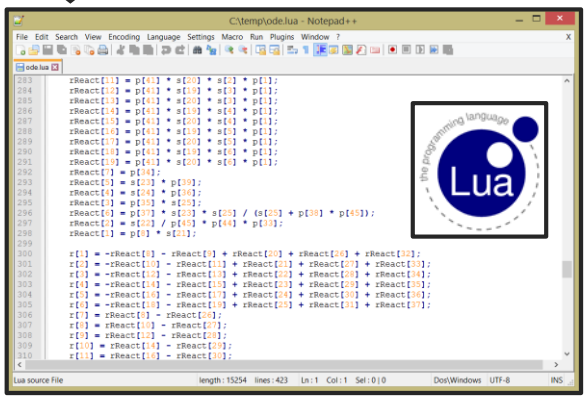
Matlab code

R code

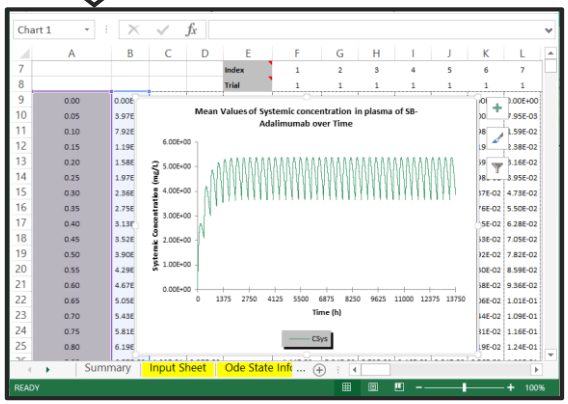
R code with equation in C

Excel file with documentation of variables, equations and parameters

IG Model code and documentation



IG Model code and PBPK variable connections in Lua



Virtual trial results in Simcyp formatted Excel file

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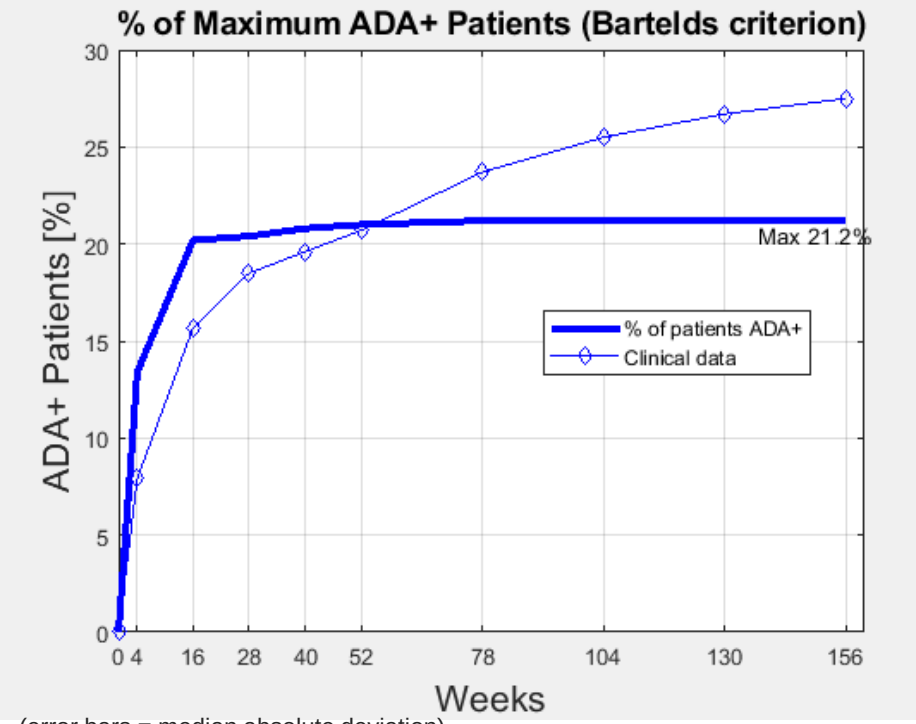
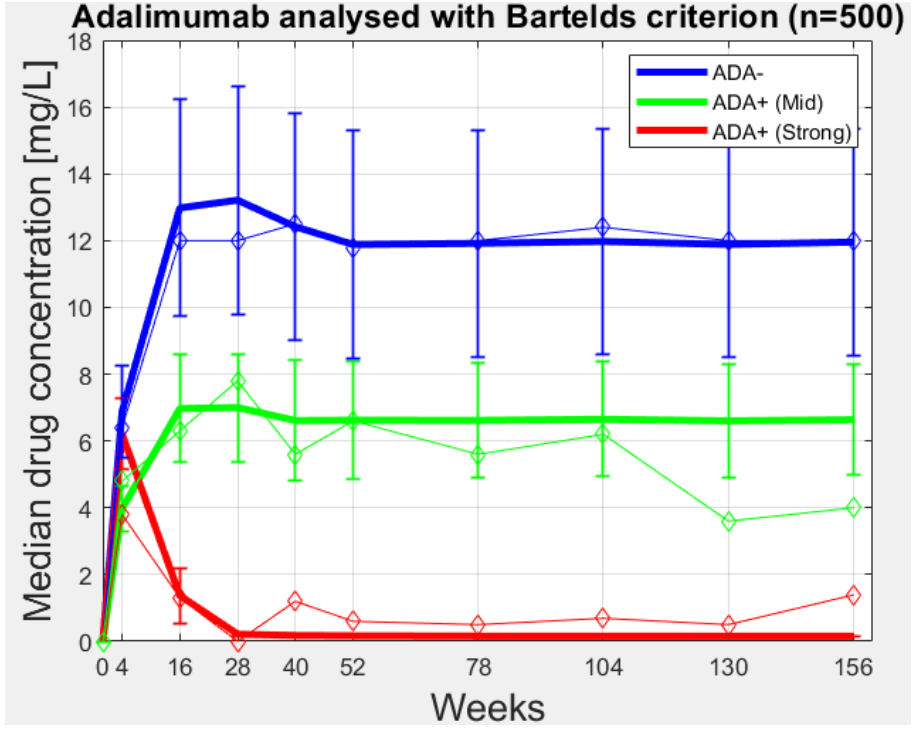
Example: Adalimumab

ADA response



(error bars = median absolute deviation)

Pharmacokinetics



ADA+ Cohort	Model	Data
ADA+ 12-100AU/ml	60%	59%
Strong ADA+ >100AU/ml	40%	41%

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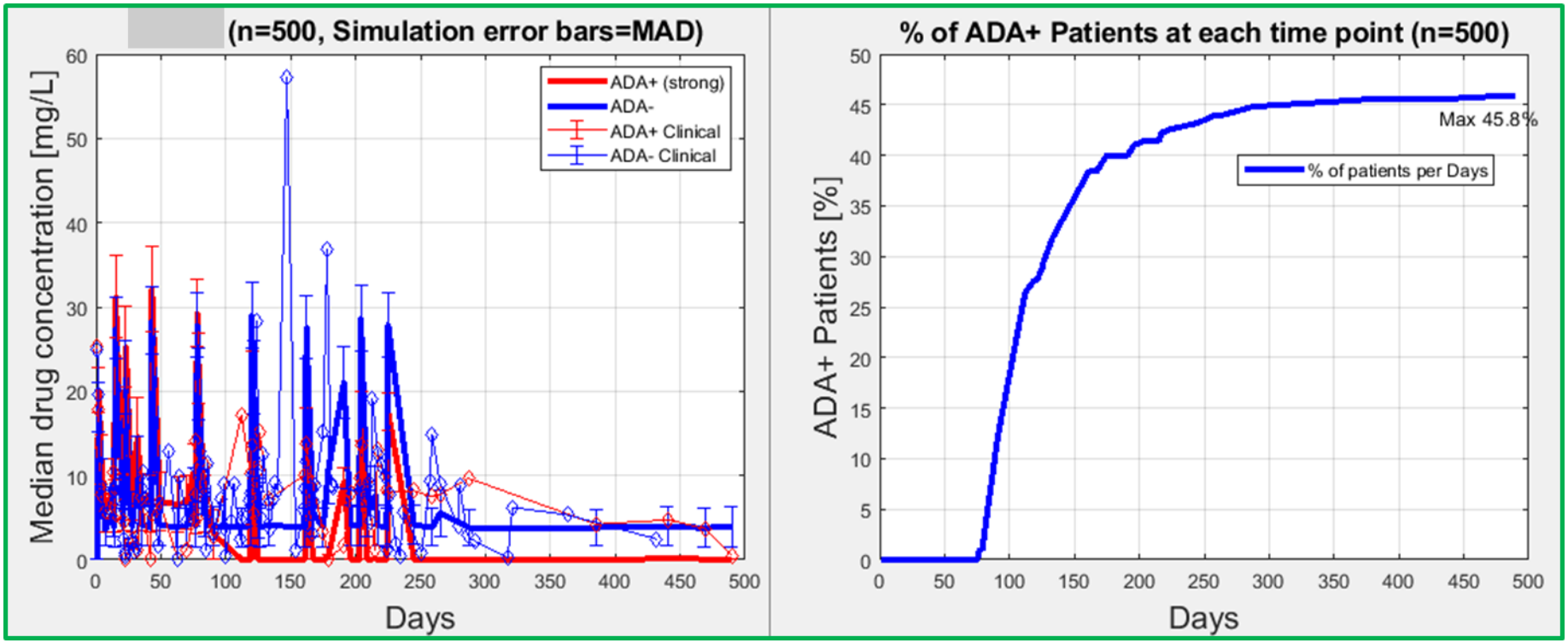
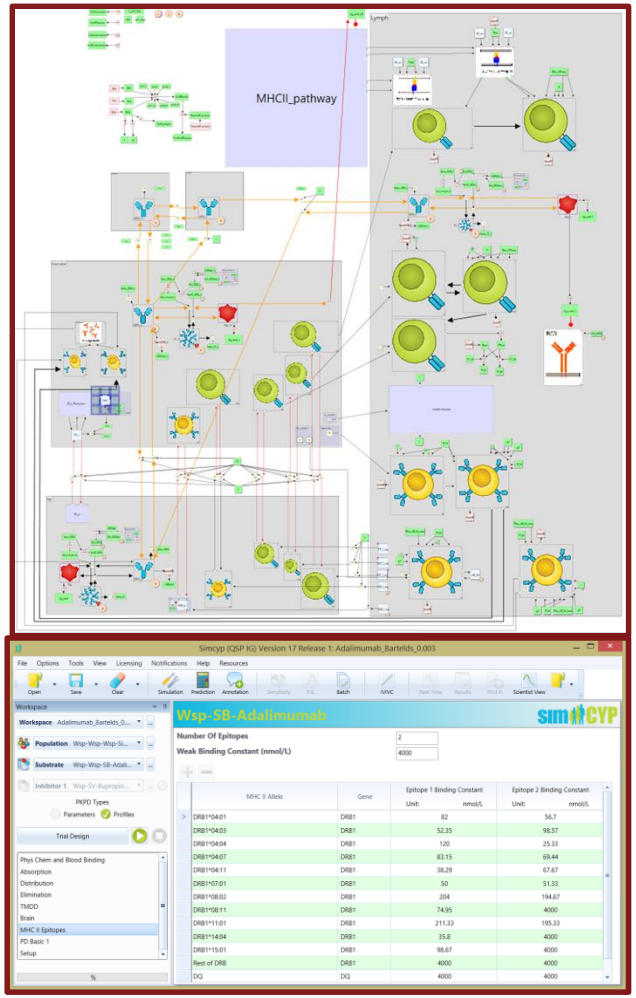
Bartelds et al., doi:10.1001/jama.2011.406

Virtual Trial Simulation of Compound X



Simulation of IG incidence (45% vs 55%) and PK for Compound X. Compound X shows considerable incidence of immunogenicity, but little influence on PK. The Adalimumab model was used as a template and compound specific parameters were calibrated by bioinformatics and comparison with Phase I data.

Applications: Extrapolation



Extrapolation to population with different HLA allele frequencies.

Personalised & Precision medicine: Prediction of PK and IG for genotyped individual.

Extrapolation to larger populations. (Phase III, IV)

IG Management: Extrapolation to different dosing regimes.

Extrapolation to paediatric population or individual children.

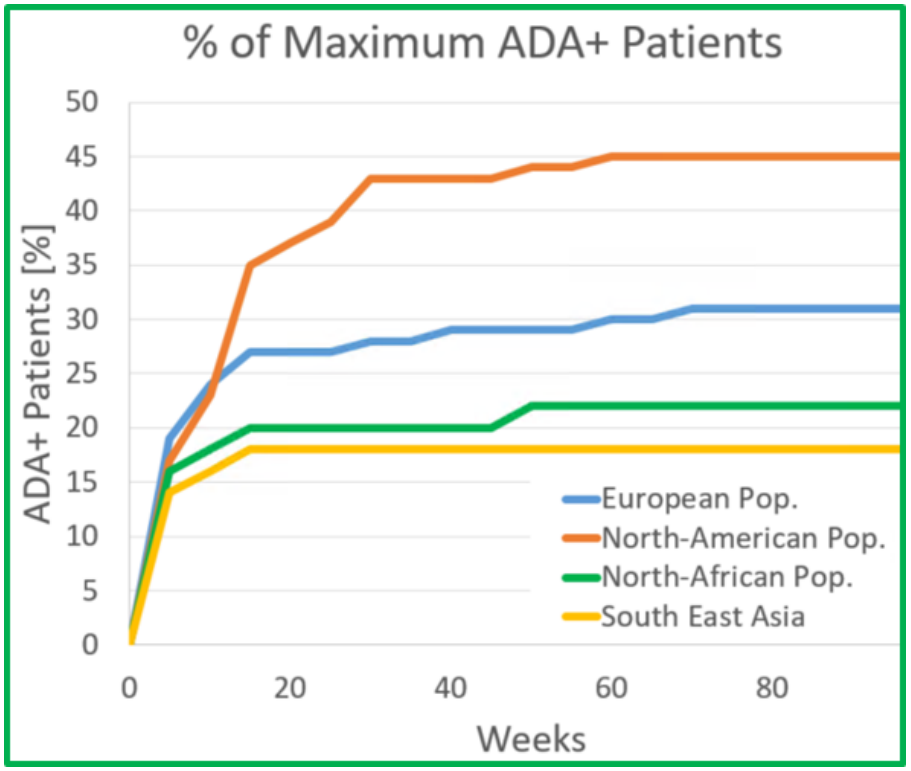
Extrapolation to disease population.

Extrapolation to age group.

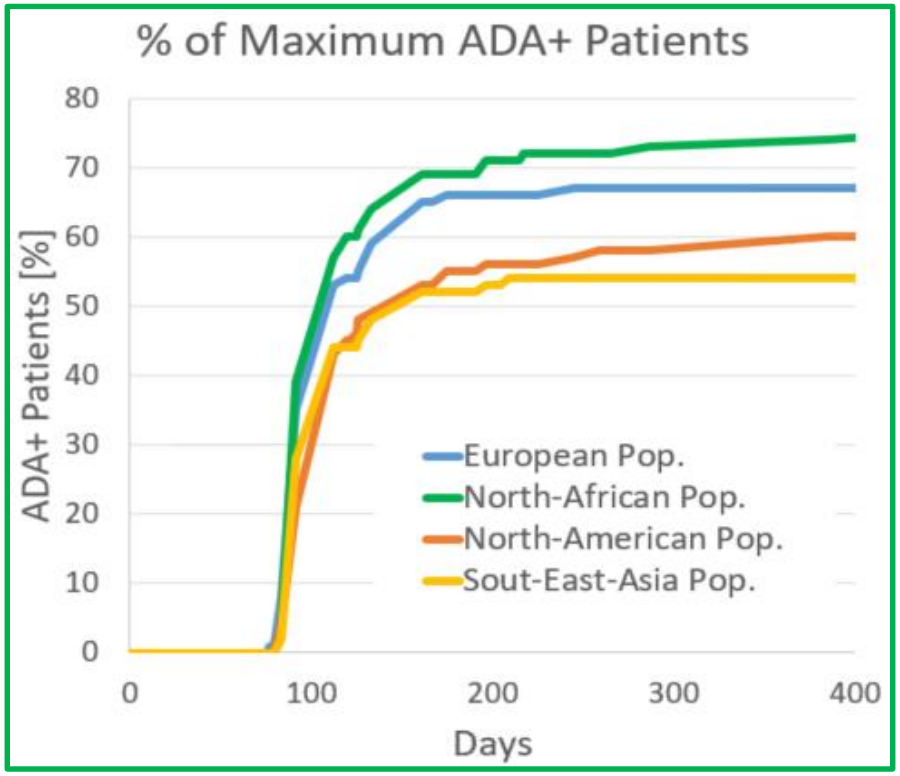
Prediction of the effect of co-therapy

Incidence of IG in different populations.

Compound 1



Compound 2



Immunogenicity is highly variable. Different compounds exhibit large differences in ADA incidence in different populations.

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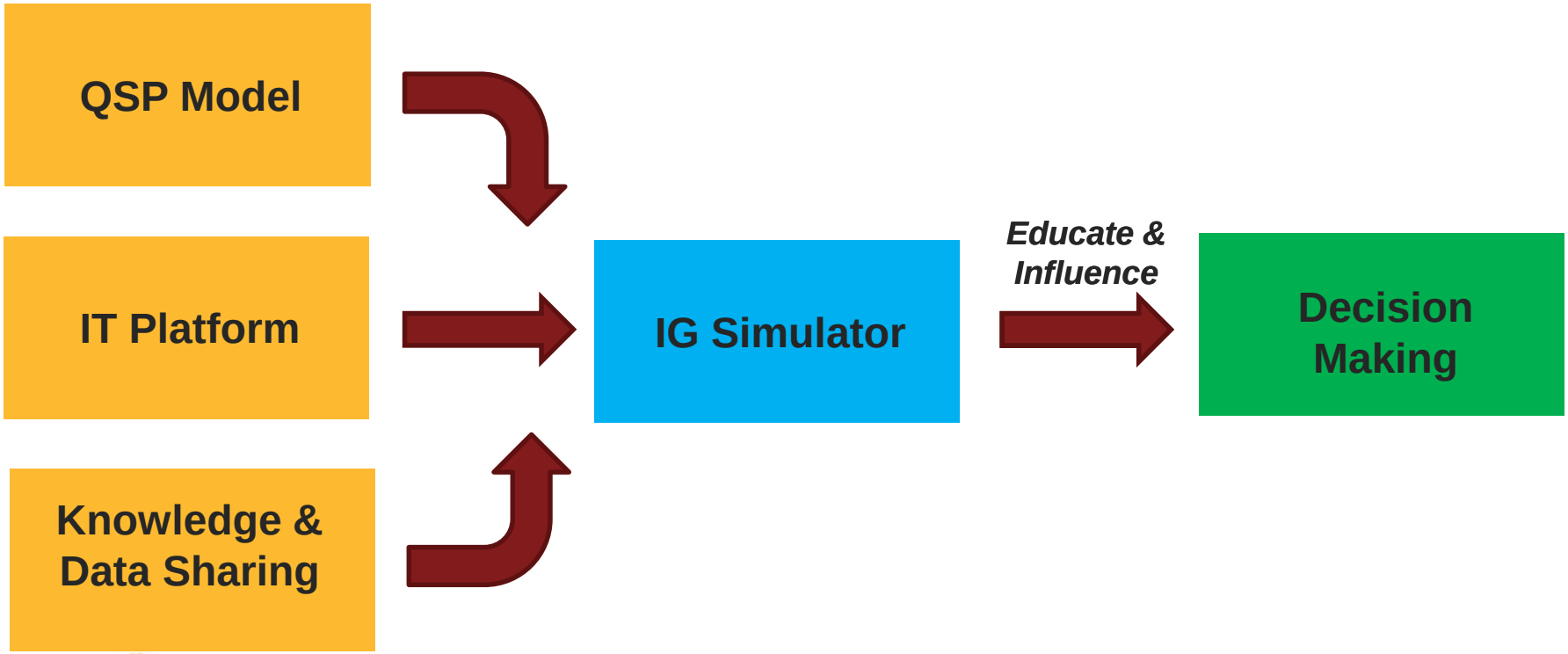
IG Consortium: overall objective

- The Consortium aims to develop the industry-standard quantitative systems pharmacology (QSP) model, coupled to a robust IT platform, to predict and manage IG and guide decision making in drug development



FDA: recent publications

A Model-Based Approach to Quantify the Time-Course of Anti-Drug Antibodies for Therapeutic Proteins

Yupeng Ren[1], Liang Li[2], Susan Kirshner[3], Yaning Wang[2], Chandrahas Sahajwalla[1] and Ping Ji[1,*]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 105 NUMBER 4 | APRIL 2019

In conclusion, our study established a model describing the time course of individual ADA titers, as well as a framework to quantify the immunogenicity of therapeutic proteins and preliminarily identified the characteristics of ADA titers and the relationship between titer and incidence of ADA. The findings from this research would be helpful to evaluate immunogenicity and its impact for new therapeutic proteins.

The AAPS Journal (2019) 21:96
DOI: 10.1208/s12248-019-0368-0

Research Article

TCPro: an In Silico Risk Assessment Tool for Biotherapeutic Protein Immunogenicity

Osman N. Yogurtcu,[1] Zuben E. Sauna,[2] Joseph R. McGill,[2] Million A. Tegenge,[1] and Hong Yang[1,3]

We validated TCPro using an experimental immunogenicity dataset, making predictions on the population-based immunogenicity risk of 15 protein-based biotherapeutics. Immunogenicity rankings generated using TCPro are consistent with the reported clinical experience with these therapeutics.

BMS: recent publication

The AAPS Journal (2019) 21: 94
DOI: 10.1208/s12248-019-0361-7

Check for updates

Research Article

Evaluating a Multiscale Mechanistic Model of the Immune System to Predict Human Immunogenicity for a Biotherapeutic in Phase 1

Lora Hamuro,[1] Giridhar S. Tirucherai,[1] Sean M. Crawford,[2] Akbar Nayeem,[3] Renuka C. Pillutla,[2] Binodh S. DeSilva,[4] Tarek A. Leil,[5] and Craig J. Thalhauser[5,6]

CONCLUSION

This study demonstrates feasibility for using a mechanistic model of the immune system that captures fundamental biology of T and B cells responses to predict anti-ATI-1465 antibody in an early trial. The model was used to predict how anti-drug antibodies impact PKPD under different dosing regimens and immunosuppressive co-medications. Having a model based framework to predict and simulate how immunogenicity might change with different doses, schedules, immune-modulating co-meds, and HLA genetic background of the patients in a clinical trial will ultimately allow prospective planning and understanding of ADA impact on PK and efficacy.

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