ASCPT

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ASCPT 2019 ANNUAL MEETING

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The Development of Consortium QSP Model of Immunogenicity with Case Examples

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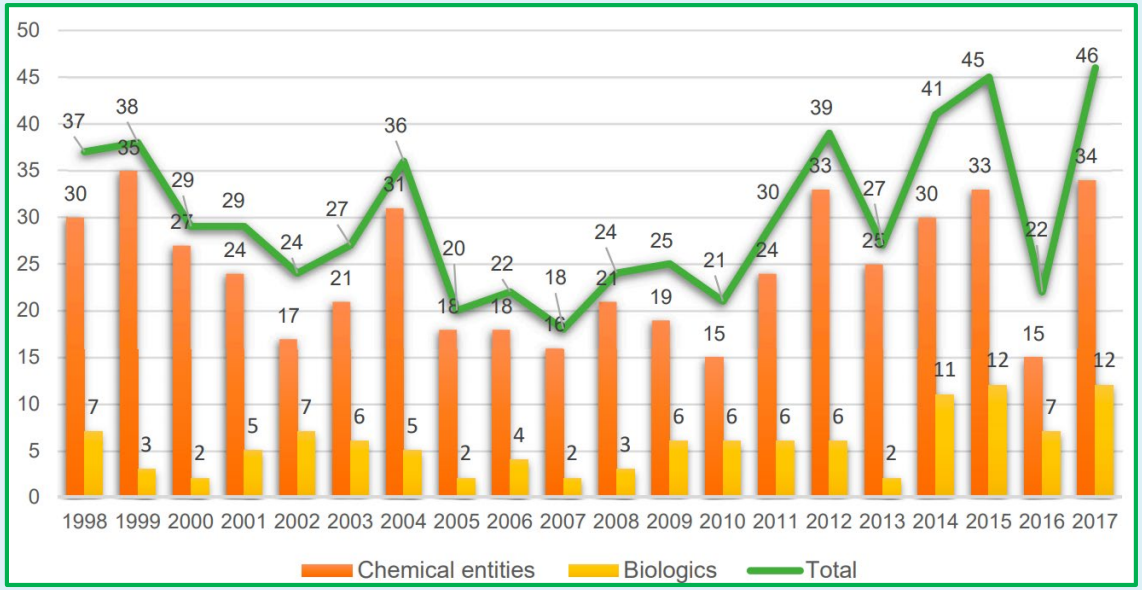
CERTARA

Biologics

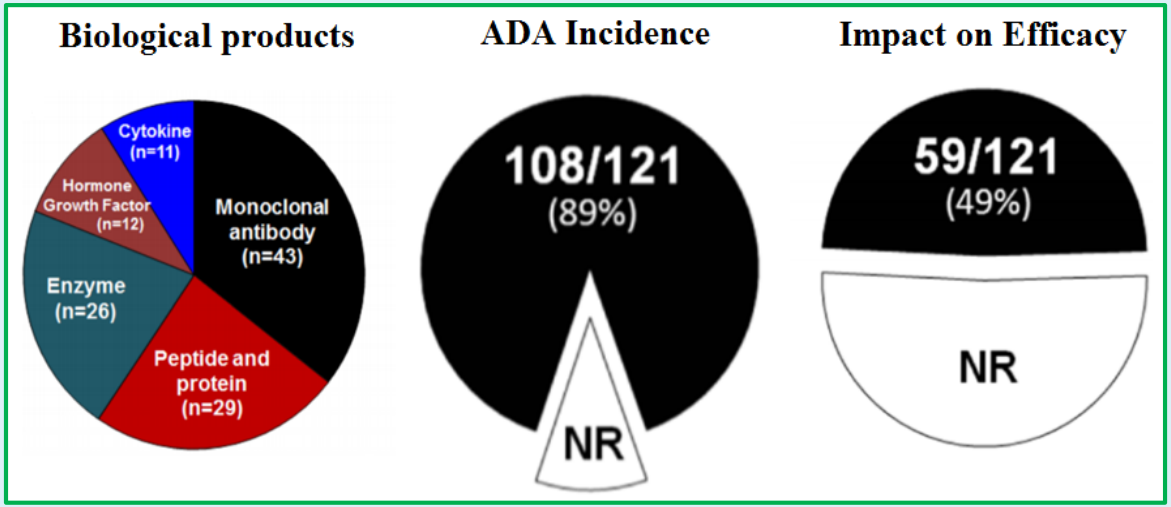


Beatriz G. de la Torre and Fernanado Albericio, Molecules, 2018

Biologics: ~30% of new drug approvals in 2017; more than half of drugs currently under development; market is forecast to reach $399.5 billions by 2025.

Immunogenicity (IG)

Study on 121 approved biologicals products



Adapted from Wang et al., AAPS J., 2016

89% incidence of immunogenicity
49% immunogenicity impact on efficacy

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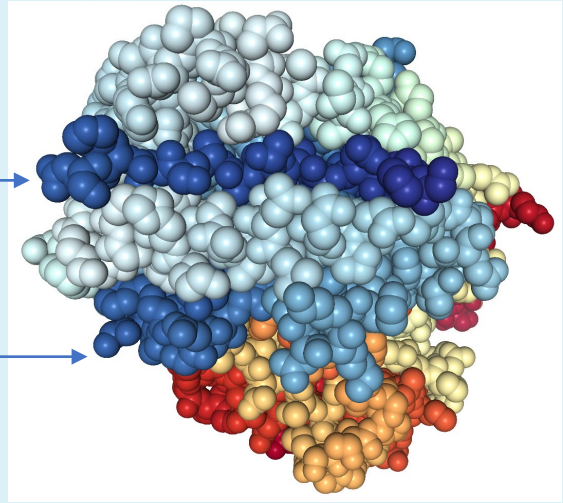
Bioinformatics



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*)	★

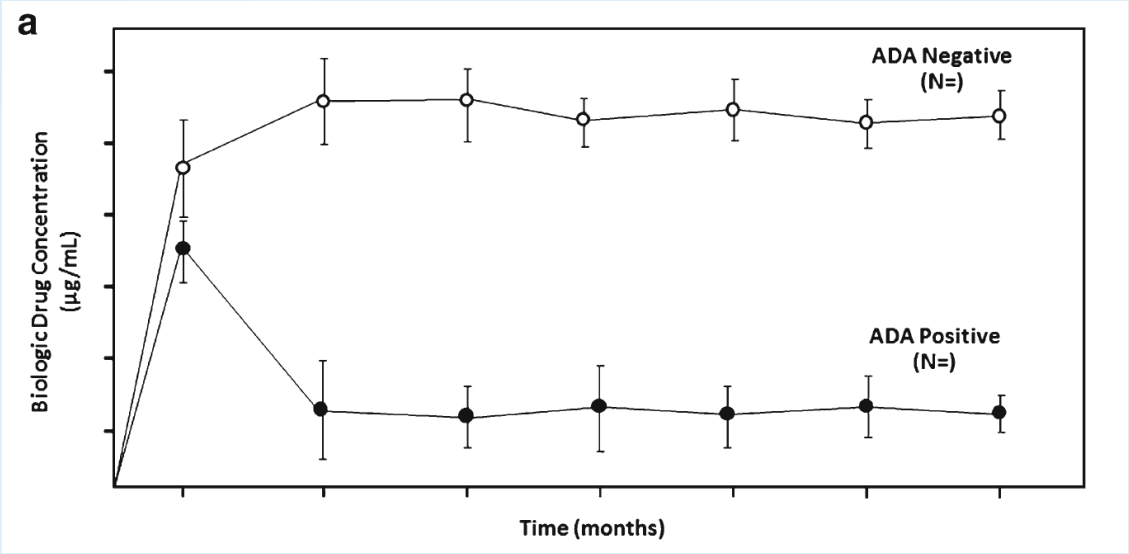
**Based on Phase II clinical study with ~200 subjects*

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).

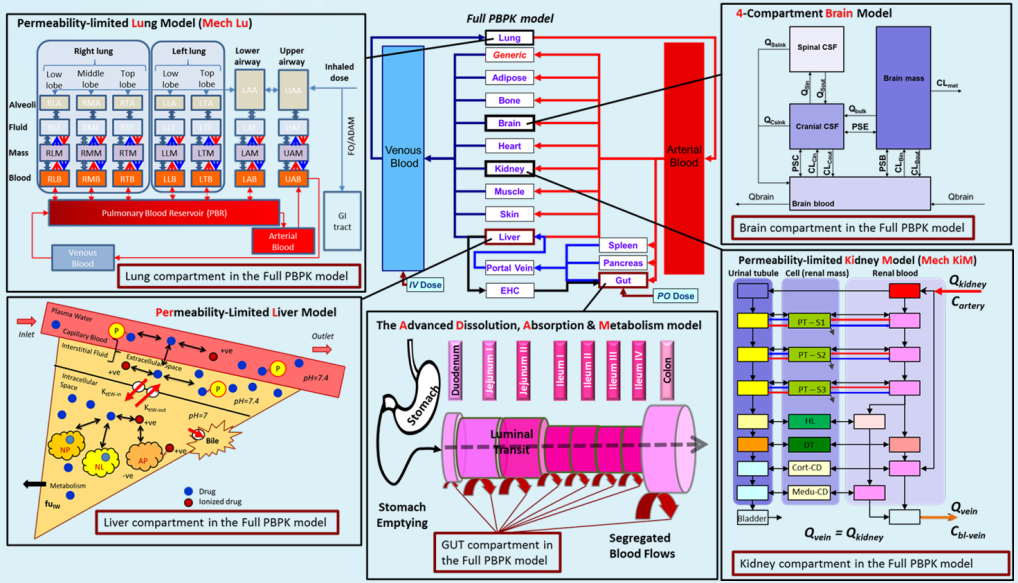
Pharmacokinetics (PK)

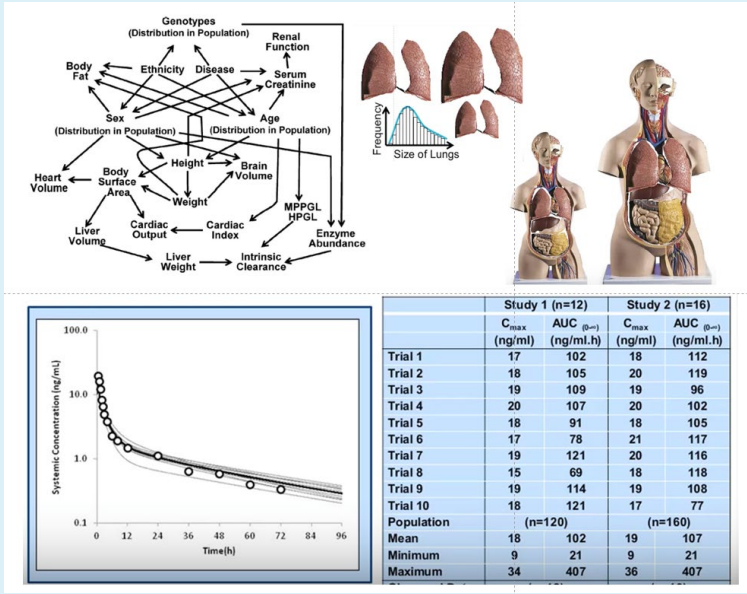


Shankar et al. Assessment and Reporting of the Clinical Immunogenicity of Therapeutic Proteins and Peptides—Harmonized Terminology and Tactical Recommendations. The AAPS Journal, Vol. 16, No. 4, July 2014 (Figure 3a).

*"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.**"*

PBPK – mechanistic modelling approach





	Study 1 (n=12)		Study 2 (n=16)	
	C_{max} (ng/ml)	$AUC_{(0-\infty)}$ (ng/ml.h)	C_{max} (ng/ml)	$AUC_{(0-\infty)}$ (ng/ml.h)
Trial 1	17	102	18	112
Trial 2	18	105	20	119
Trial 3	19	109	19	96
Trial 4	20	107	20	102
Trial 5	18	91	18	105
Trial 6	17	78	21	117
Trial 7	19	121	20	116
Trial 8	15	69	18	118
Trial 9	19	114	19	108
Trial 10	18	121	17	77
Population	(n=120)		(n=160)	
Mean	18	102	19	107
Minimum	9	21	9	21
Maximum	34	407	36	407

Full Simcyp PBPK model contains about 450 variables. Since 2012 Simcyp team scrutinised about 15,000 articles to inform the model.

Computer simulation of virtual clinical trial.

PBPK – mechanistic modelling approach

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use IMBRUVICA safely and effectively. See full prescribing information for IMBRUVICA.

IMBRUVICA® (ibrutinib) capsules, for oral use

Initial U.S. Approval: 2013

Drug Interactions

Coadministration of Ibrutinib with CYP3A Inhibitors

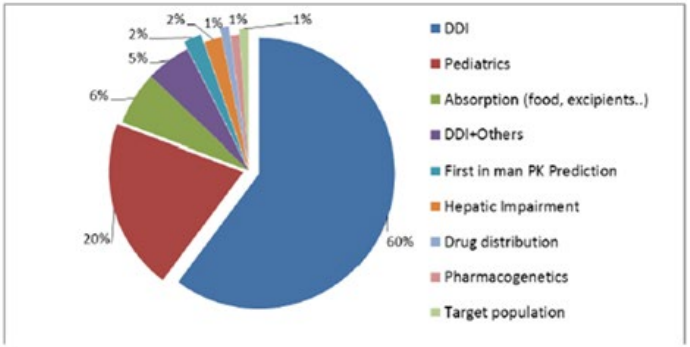
In a sequential design trial of 18 healthy, fasted volunteers, a single dose of 120 mg of IMBRUVICA was administered alone on Day 1 and a single dose of 40 mg of IMBRUVICA was administered on Day 7 in combination with 400 mg of ketoconazole (given daily on Days 4 - 9). Ketoconazole increased ibrutinib dose-normalized C_{max} and AUC 29-fold and 24-fold, respectively. Simulations using fasted conditions indicate that moderate CYP3A inhibitors diltiazem and erythromycin may increase AUC of ibrutinib by 5- to 8-fold.

Coadministration of Ibrutinib with CYP3A Inducers

PK data from a dedicated drug interaction trial showed that rifampin (a strong CYP3A inducer) decreases ibrutinib C_{max} and AUC by more than 13- and 10-fold. Simulations using PBPK suggested that a moderate CYP3A inducer (efavirenz) may decrease the AUC of ibrutinib by up to 3-fold.

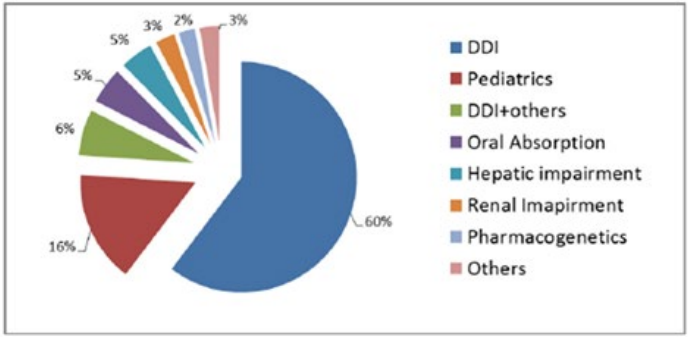
41 Labels with *in-silico* substitutes for clinical data informed by Simcyp

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

Certara IG QSP Consortium

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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.

abbvie

Lilly

Bristol-Myers Squibb

Pfizer

astellas
Leading Light for Life

Roche
Genentech
A Member of the Roche Group

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

IG Model

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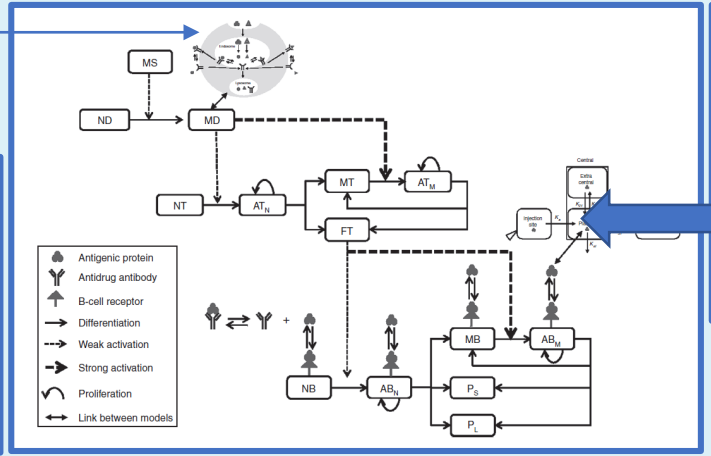
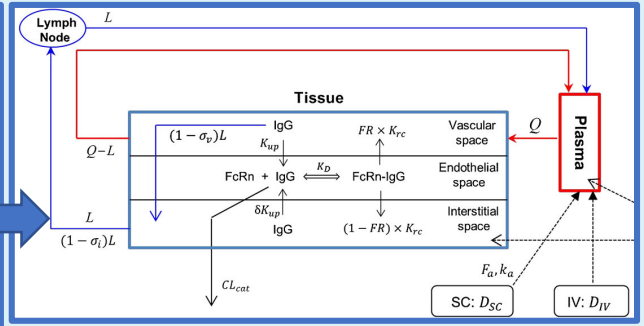
Immune response (Pfizer).
(Chen et al., CPT PSP (2014) 3, e134)

Simcyp biologics PBPK.
(Li et al., AAPS Journal (2014), 16, 1097)

MHC-II allele	Allele frequency in North America	Epitope 1 binding affinity (nmol/l)	Epitope 2 binding affinity (nmol/l)
DRB1*04:01	0.089	123	85
DRB1*04:03	0.053	78.52	147.85
DRB1*04:04	0.036	180	38
DRB1*04:07	0.085	124.73	104.16
DRB1*04:11	0.15	57.44	101.5
DRB1*07:01	0.0083	75	77
DRB1*08:02	0.069	306	292
DRB1*08:11	0.0015	112.43	4,000
DRB1*11:01	0.0436	317	293
DRB1*14:04	0.00075	53.7	4,000
DRB1*15:01	0.0083	148	4,000
Rest of DRB1 alleles	0.46	4,000	4,000





Bioinformatics (IEDB)

Integration & IT development

IG Model V1 (Q1 2018)

Biological scope expansion

IG Model V2 (Q1 2019)

Validation

IG Model V3 (Q1 2020)

IG Simulator

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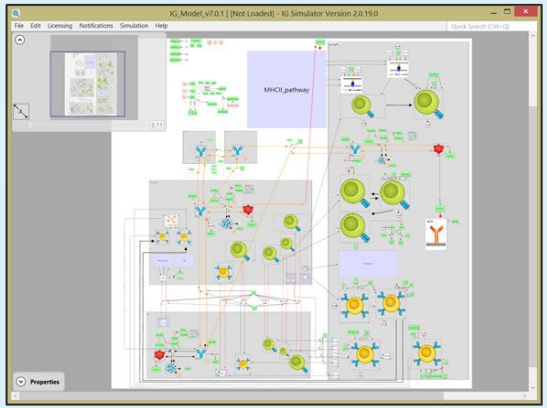
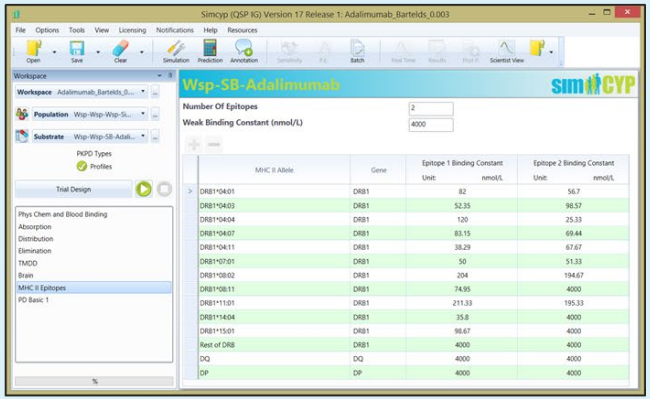
Biological Process Map interface



Read workspace file.

Simcyp simulator



Export IG Model code.

Write IG Model

Read IG Model and augment ODEs

Simulate virtual trial and output results.

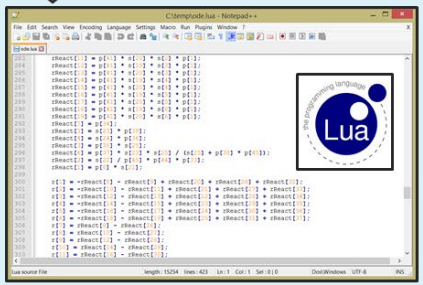
Matlab code

R code

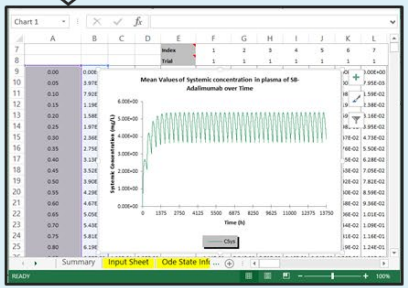
R code with equation in C

Excel file with documentation of variables, equations and parameters

IG Model code and documentation



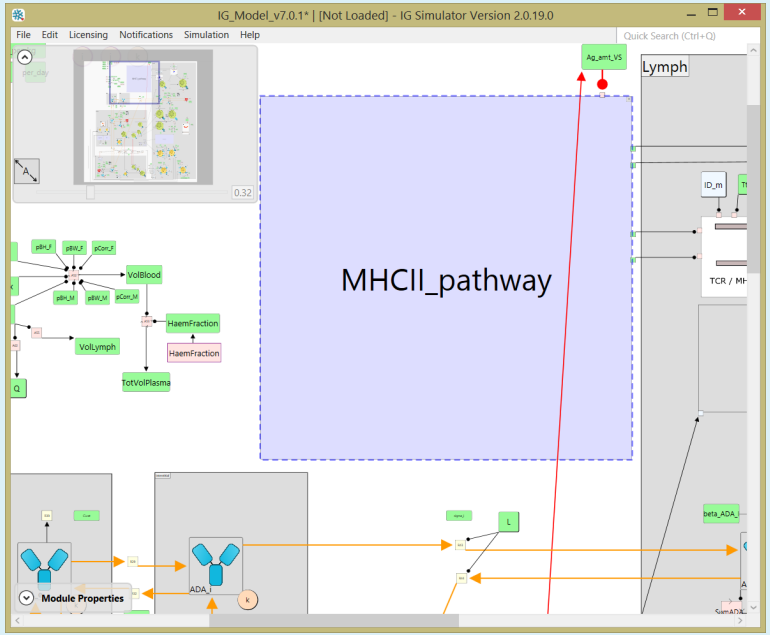
IG Model code and PBPK variable connections in Lua

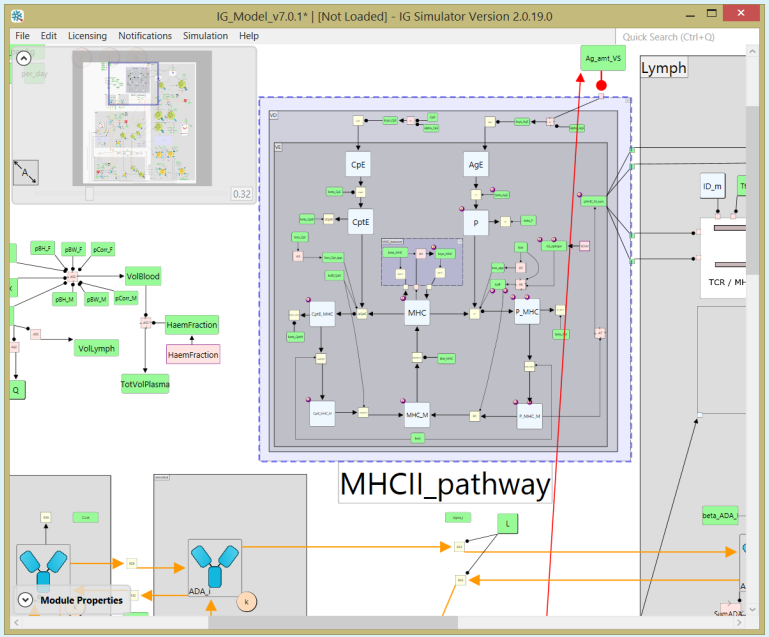


Virtual trial results in Simcyp formatted Excel file

Modular Biological Process Map interface

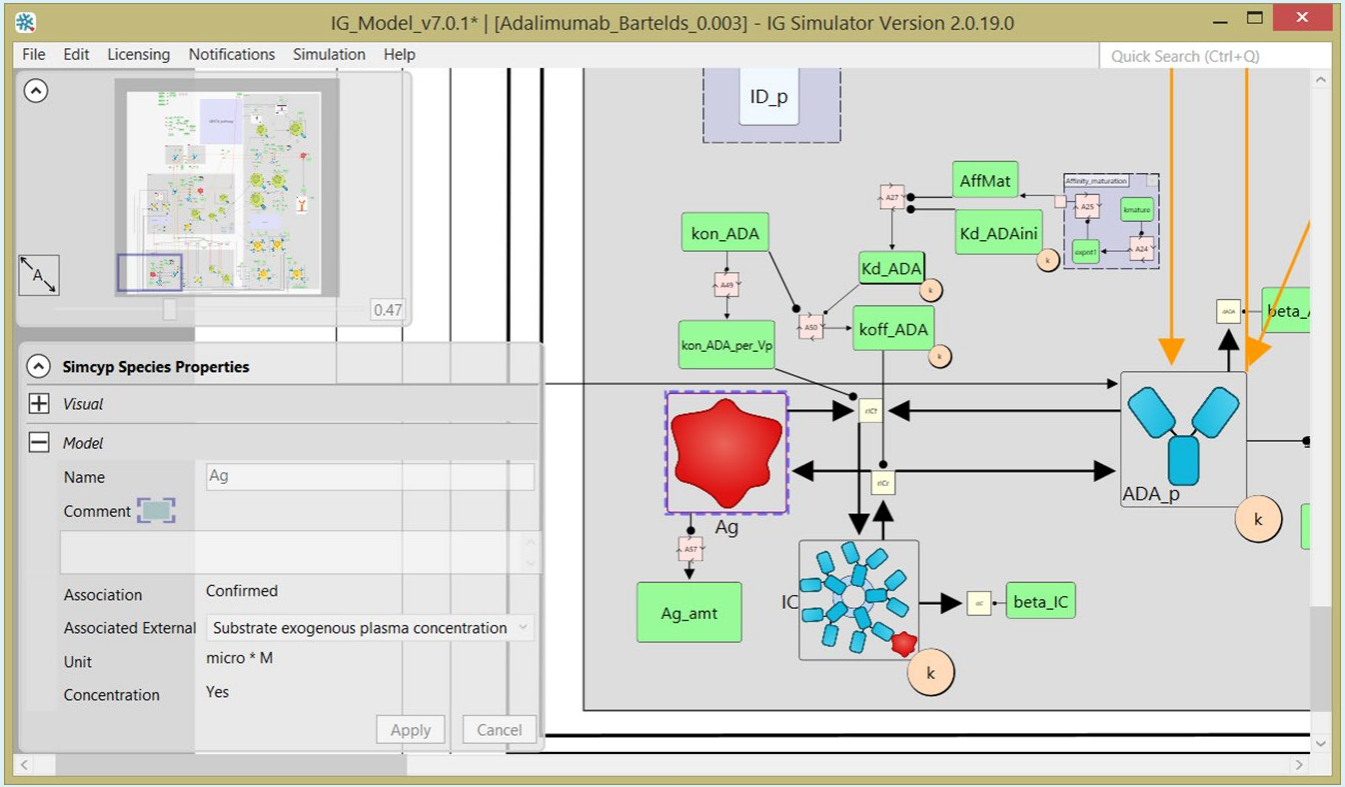
- Modules encapsulate complex mechanisms which are connected to the model through well defined interfaces.
- This facilitates both visualisation and consortium team development of multiscale mechanistic models.



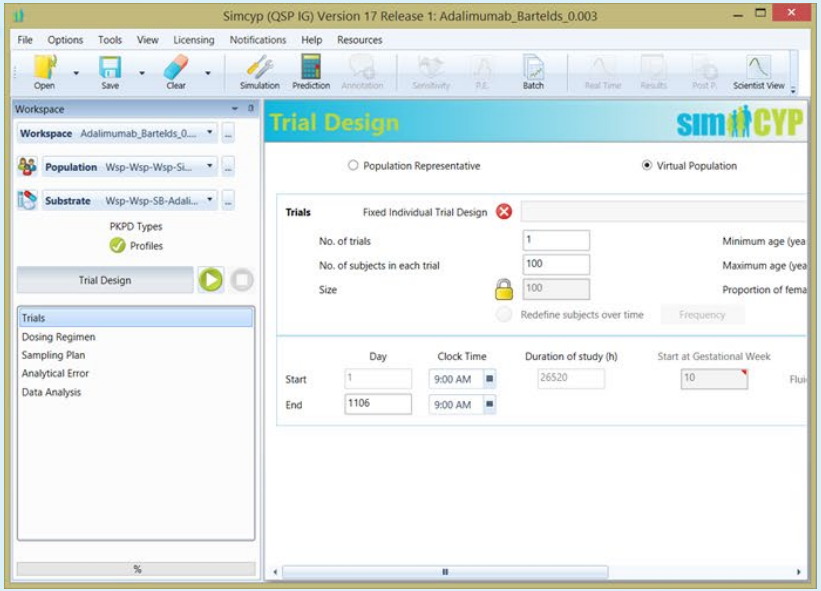


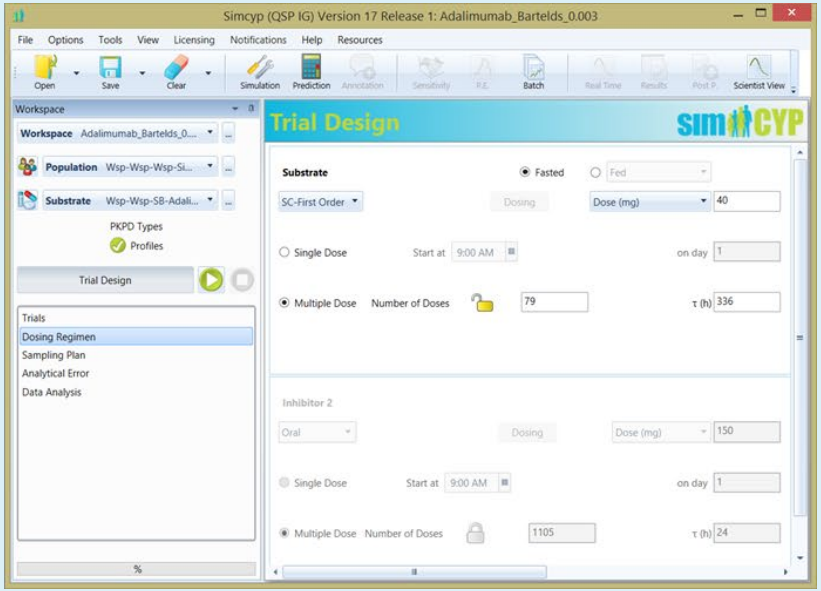
Connection to Simcyp PBPK model.

- Specie “Ag” in biological process map is merged with variable “Substrate exogenous plasma concentration” in Simcyp PBPK.
- The ODE for Simcyp variable is augmented by rate laws of ADA binding and Immune Complex dissociation.



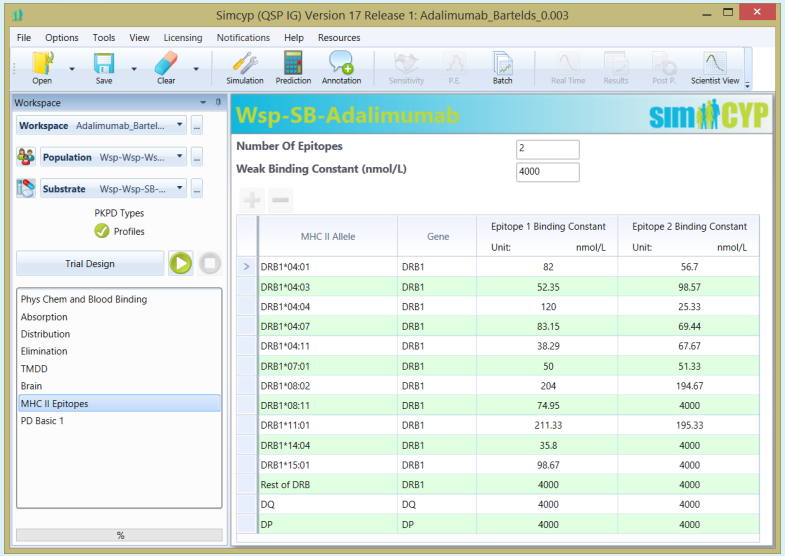
Virtual trial design.

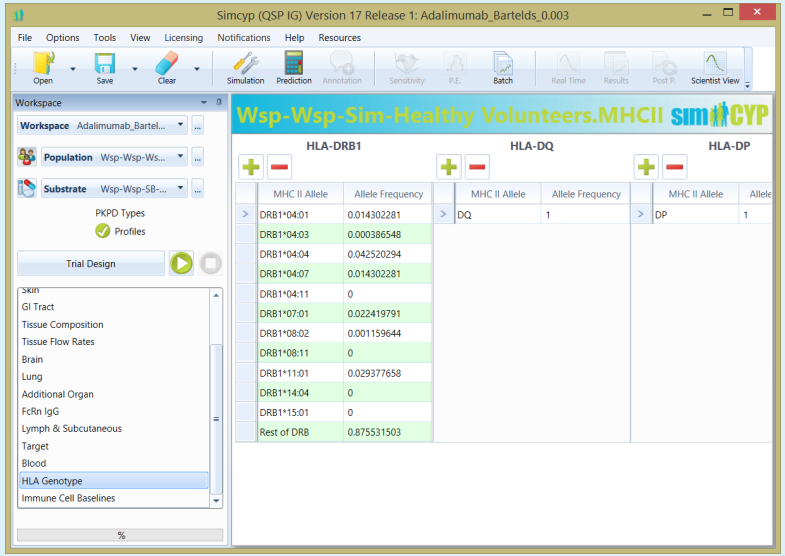




- Simcyp simulator is modularised into System, Compound, Population and Trial design.
- Trial screens specify number of subjects from target Population and dosing regime of the Compound.

Simcyp simulator with Immunogenicity screens





- The compound section of Simcyp biologics model has been expanded to allow input of antigenic peptide binding constants.
- Population section of Simcyp has been expanded to allow input of allele frequencies used to generate MHC II binding constants.

Virtual trial simulation: Adalimumab example

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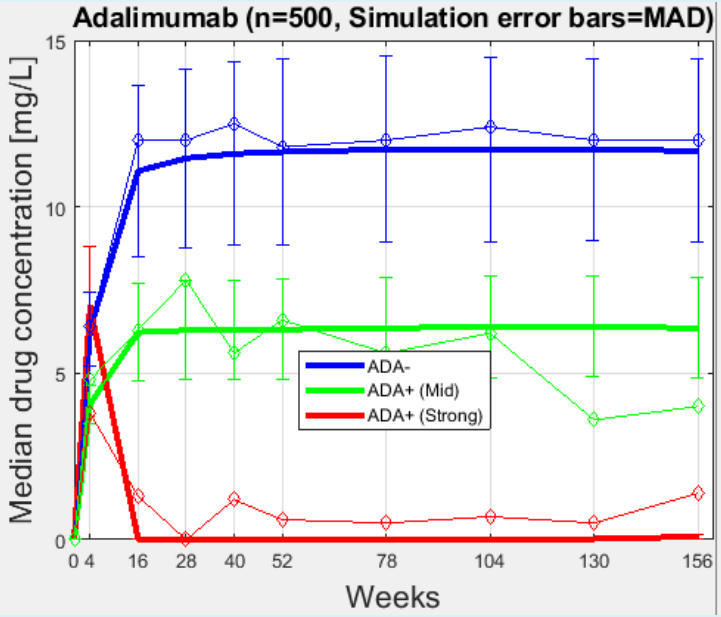
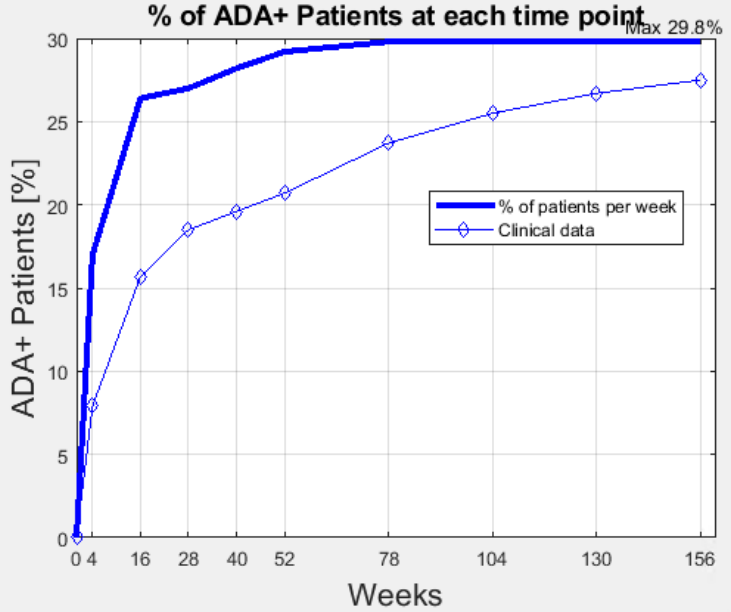
Simulation of Adalimumab clinical trial of Bartelds et al., JAMA 2011





Simulation

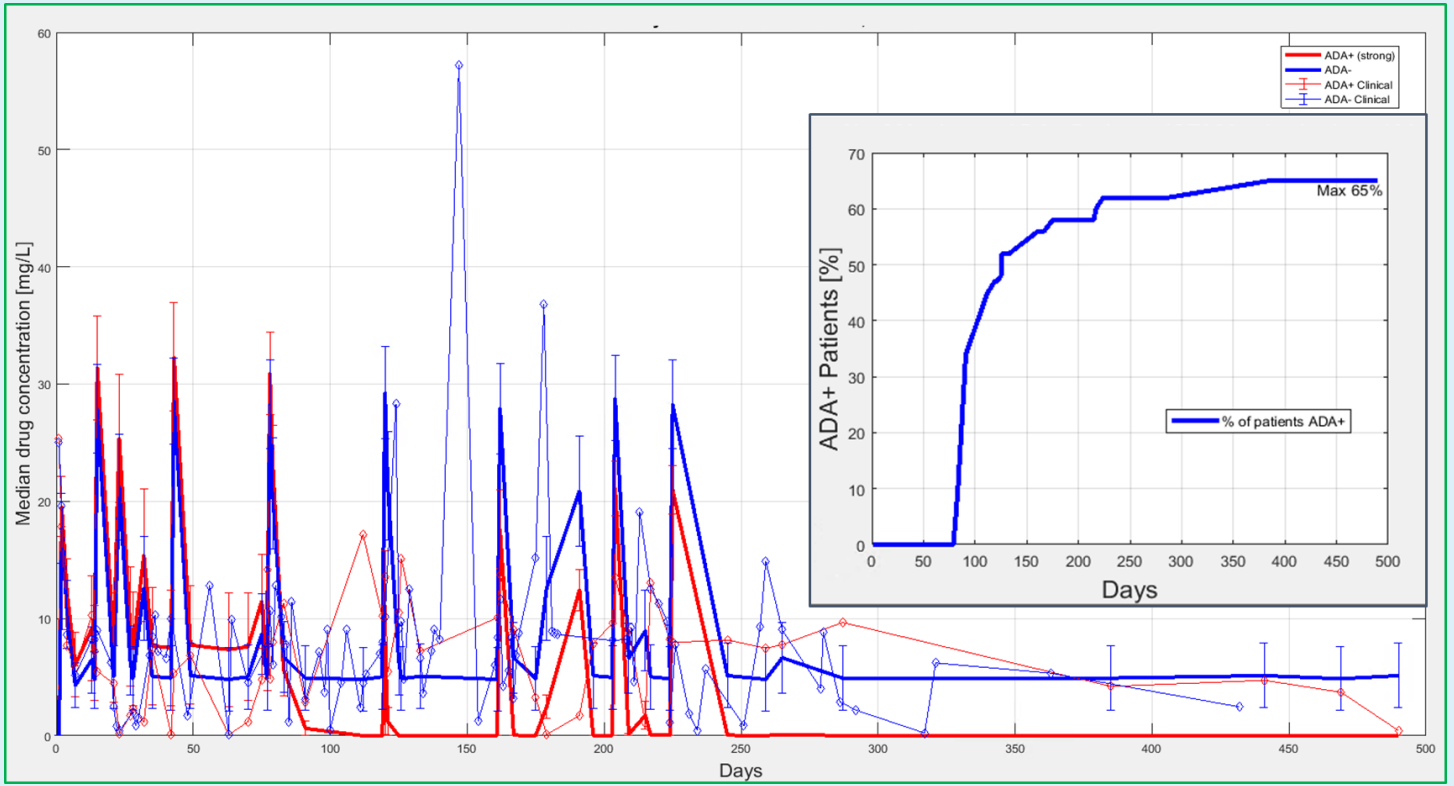
Number of ADA+ Mid = 70%
Number of ADA+ Strong = 30%

Clinical Data

Number of ADA+ Mid = 60%
Number of ADA+ Strong = 40%

Compound X: IG does not impact PK

- Phase II clinical trial for Compound X.
- Production of ADAs is observed in 65% of subjects.
- There is no impact on drug plasma concentration.



Incidence of IG in different populations.

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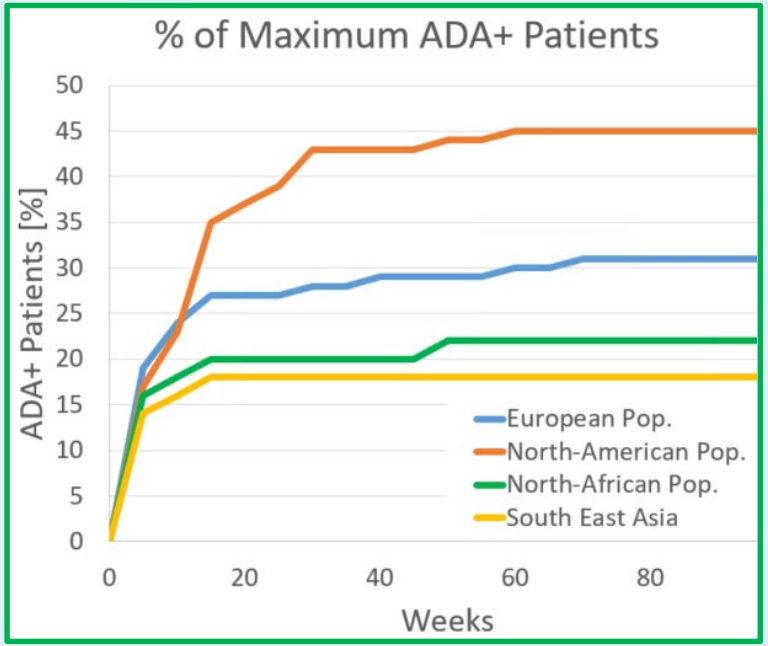
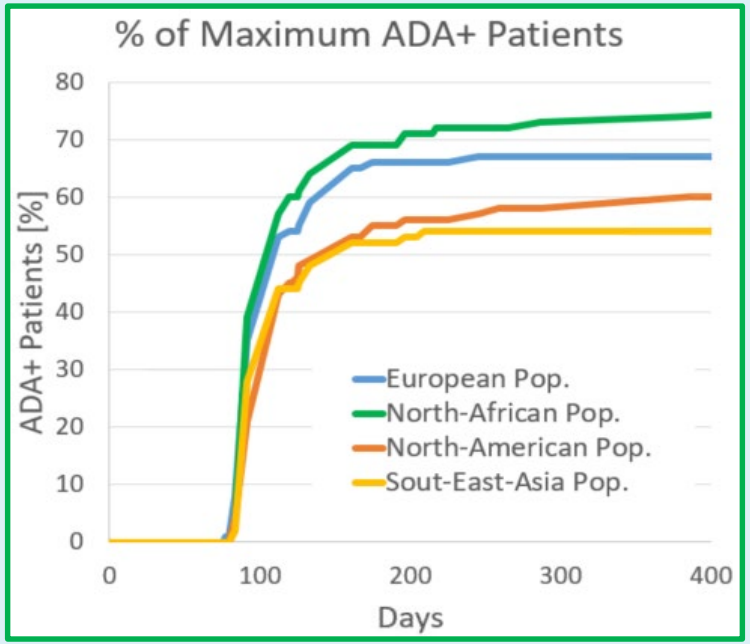
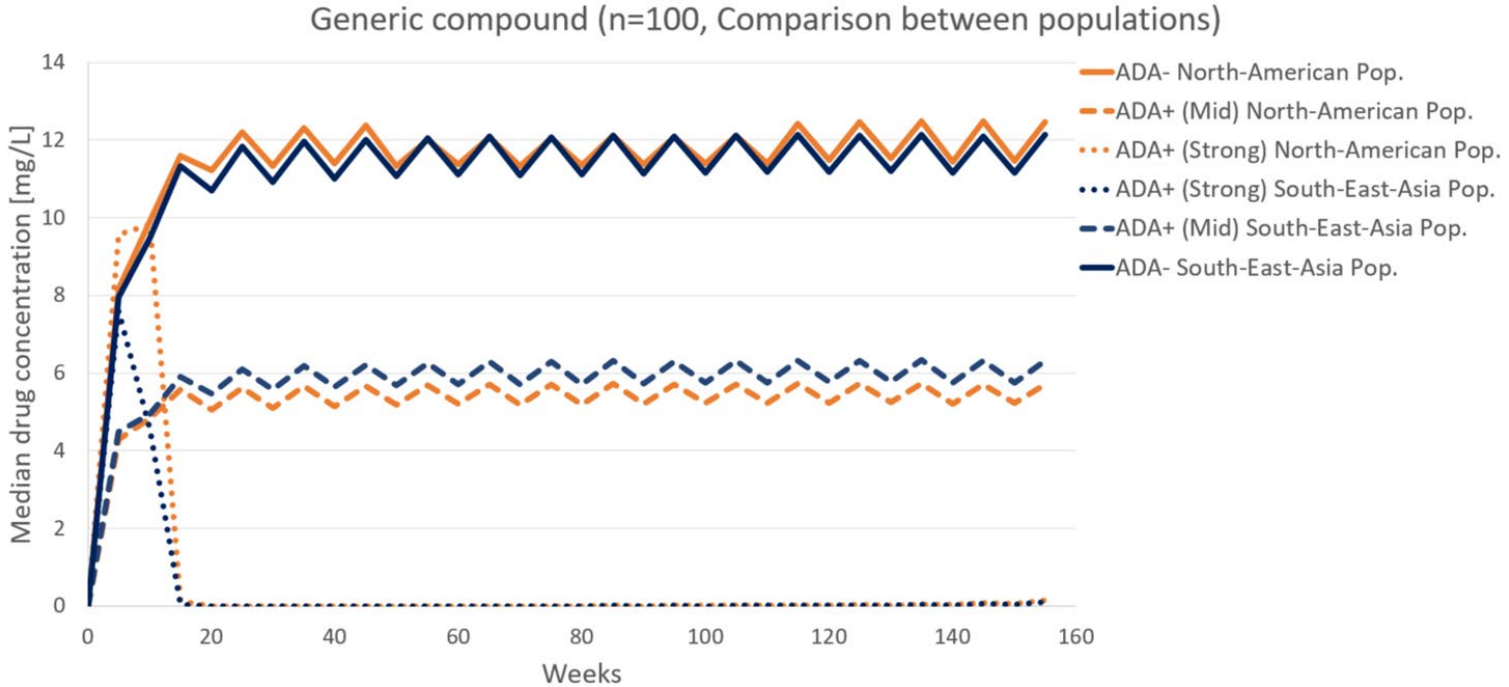
Compound X



Compound Y



PK in different populations



Application of IG Simulator

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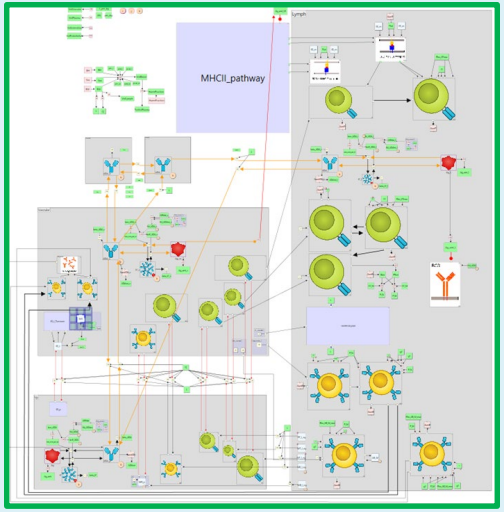
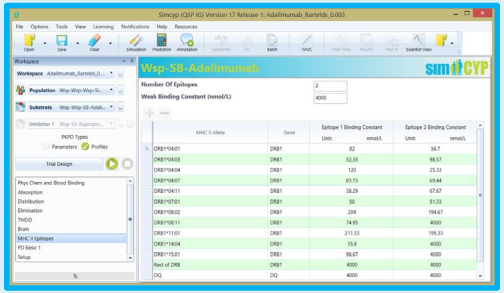
Immune response model



Simcyp PBPK



- Prediction of PK and ADA from sequence and in-vitro assays.
- 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.

Acknowledgements

- **Abbvie**
- **Astellas**
- **BMS**
- **Genentech/Roche**
- **Lilly**
- **Pfizer**

Certara IG Consortium team

Leadership

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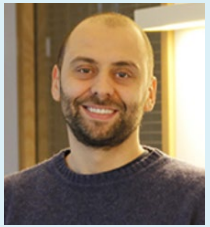
Piet van der Graaf
SVP and Head of QSP

Neil Benson
Head of QSP Operations

IG Model



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