


A large, colorful molecular structure graphic is positioned on the left side of the image. It features various colored spheres (blue, red, green, yellow, orange, pink, white) connected by thin white lines, representing atoms and bonds. The structure is set against a light blue background with a faint silhouette of a human head in profile, suggesting the connection between molecular science and human health.

FROM
MOLECULE TO
PATIENT

ASCPT 2019
ANNUAL MEETING



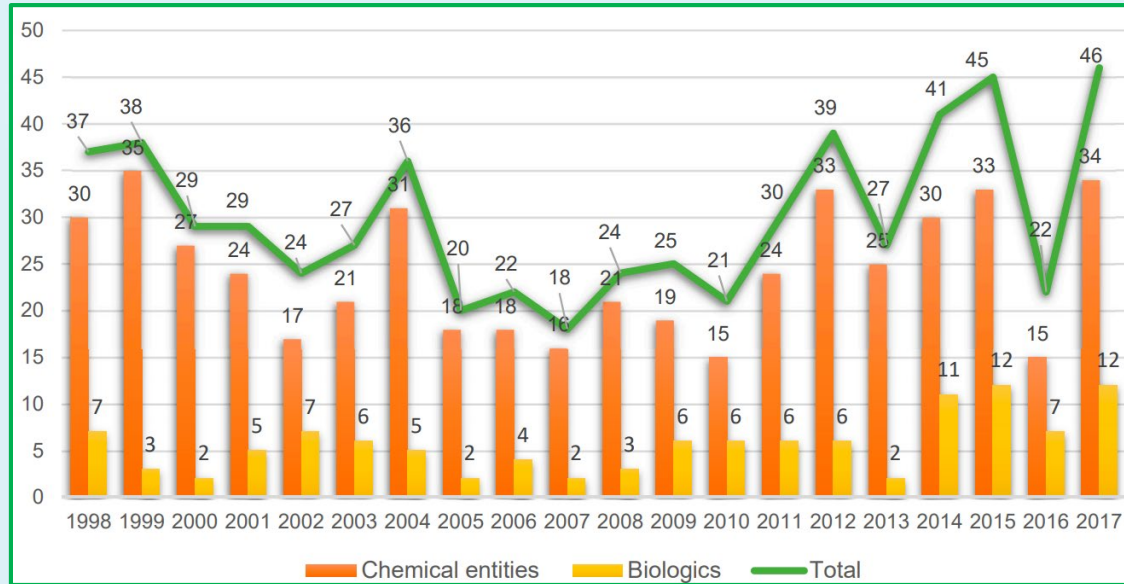
The Development of Consortium QSP Model of Immunogenicity with Case Examples

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Biologics

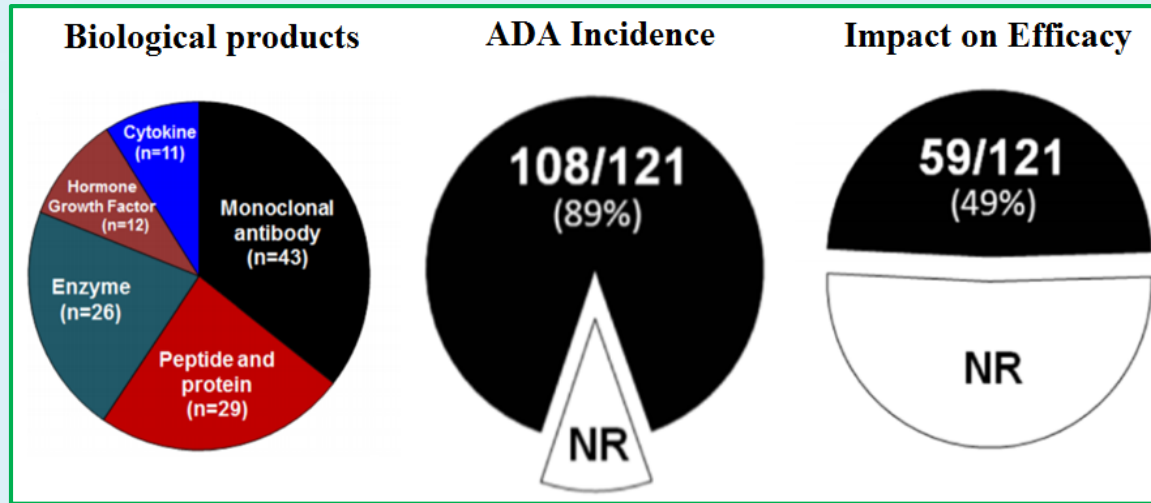


Beatriz G. de la Torre and Fernando Albericio, Molecules, 2018

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)

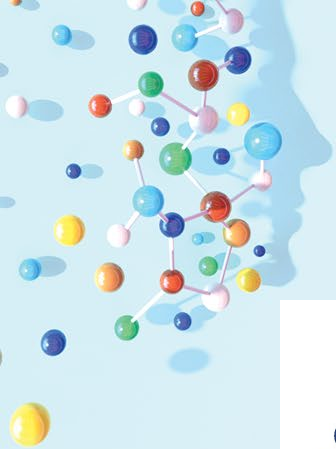
Study on 121 approved biologicals products



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

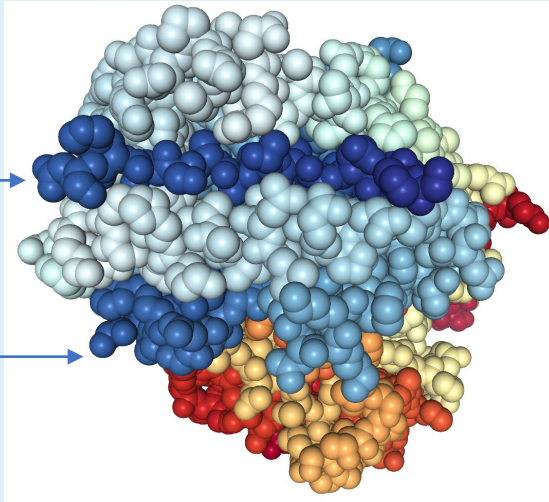
89% incidence of immunogenicity
49% immunogenicity impact on efficacy

Bioinformatics



Antigenic peptide

MHC II receptor



IG is mostly tackled preclinically:

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

Genentech
A Member of the Roche Group

(Kapil Gadkar & Jennifer Rohrs)

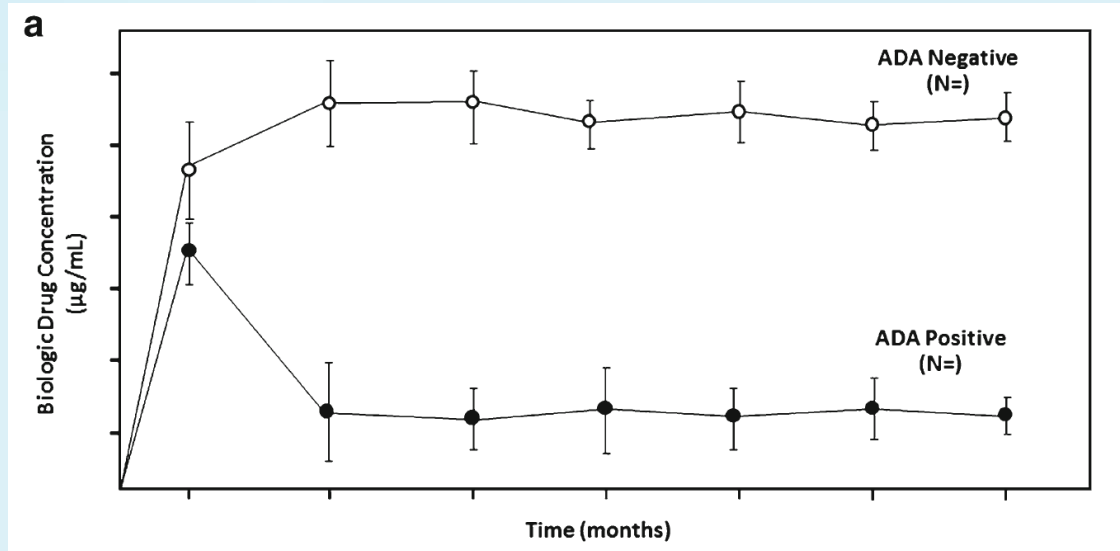
Antibody Drug	# Binding peptides*	# MHC II alleles	% ADA+ Patients
Bococizumab (Pfizer)	2	12	68% (Ridker, 2017)
Alirocumab (Regeneron)	1	1	5.1% (Roth, 2017)
Evolocumab (Amgen)	0	0	0.1% (Henry, 2016)
GNE anti-PCSK9 (Genentech)	2	8	4% (GENE data*)



*Based on Phase II clinical study with ~200 subjects

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).

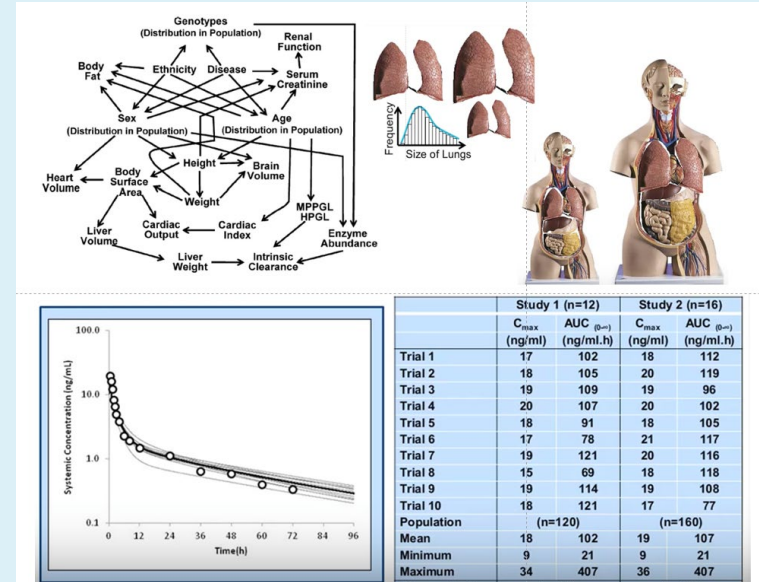
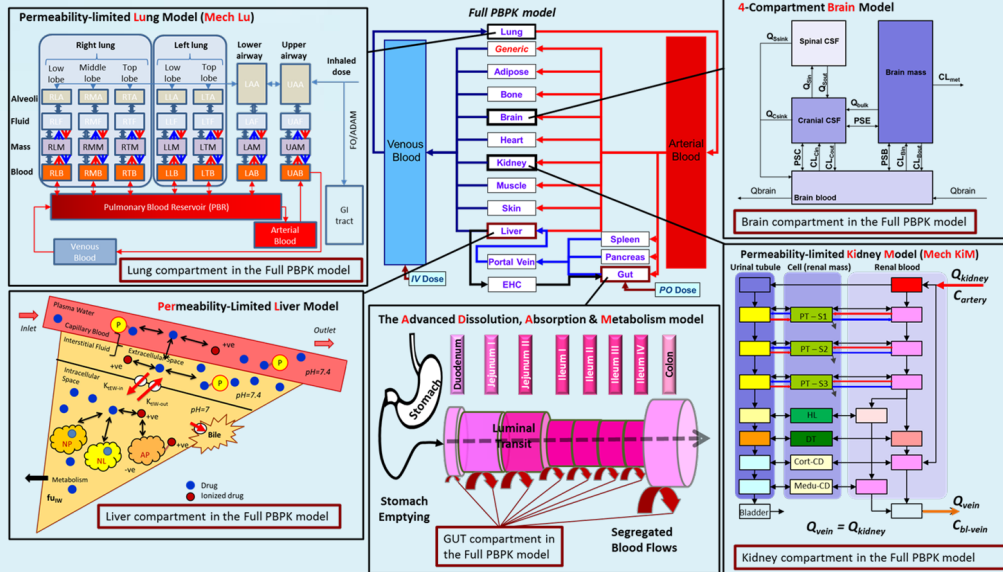
Pharmacokinetics (PK)



“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.**”

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).

PBPK – mechanistic modelling approach



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

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.

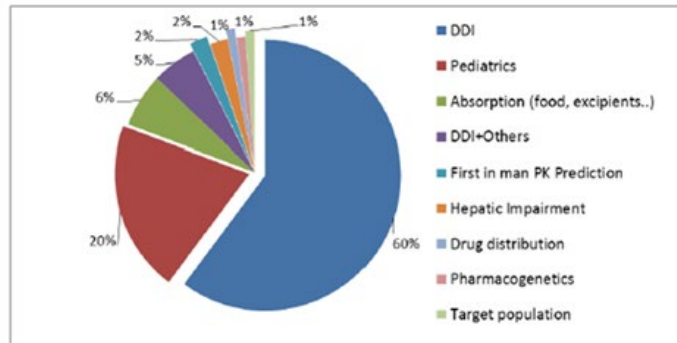
Coadministration of Ibrutinib with CYP3A Inducers

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.

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 Olanzapine (Bancinib) Rheumatoid Arthritis
Novartis Odomzo (Sonidegib) Basal Cell Carcinoma	Janssen Olysio (Simeprevir) Hepatitis C	Actelion Opsumit (Macitentan) Pulmonary Arterial Hypertension	Pharmacycics Imbruvica (Ibrutinib) Mantle Cell Lymphoma and Chronic Lymphocytic Leukemia	AstraZeneca Movalant (Naloxegol) Opioid Induced Constipation	Genentech Cotelic (Cobimetinib) Metastatic Melanoma
Genzyme Cerdelga (Efgartigimod) Gaucher Disease	Sanoft	Novartis	Pfizer	Alkermes	AstraZeneca a (Dipeptidyl) and Ovarian Cancer
Novartis Farydak (Panobinostat) Multiple myeloma	Intercept	Actelion	Janssen	Merck	Merck Steglan (Erlugliflozin) Type 2 Diabetes
Eli Lilly Verzenio (Abemaciclib) Metastatic Breast Cancer	Actelion Ocaliva (Obeticholic acid) Primary Biliary Cholangitis	Actelion Ultram (Salsipreg) Pulmonary Arterial Hypertension	Janssen Invokana (Canagliflozin) Type 2 Diabetes	Merck Prevymis (Letermovir) Cytomegalovirus	Merck
Novartis Kisqali (Ribociclib succinate) Metastatic Breast Cancer	PTC Therapeutics Emflaza (Deflazacort) Duchenne Muscular Dystrophy	Shionogi Symproic (Naldemedine) Opioid Induced Constipation	Spectrum Beleodag (Belmostat) Peripheral T-cell Lymphoma	UCB Briavect (Briaracetam) Epilepsy	Vertex Symdeko (Tezacaftor/ivacaftor) Cystic Fibrosis
Novartis Rydapt (Midostaurin) Acute Myeloid Leukemia	Ariad Aurbrig (Brigatinib) Metastatic Non-small Cell Lung Cancer	Janssen Eriqada (Apalutamide) Non-metastatic Prostate Cancer	Helsinn Akynzeo (fosnetupitant/palonosetron) Acute and Delayed Nausea	AkaRx Doptelet (Avatrombopag maleate) Thrombocytopenia	

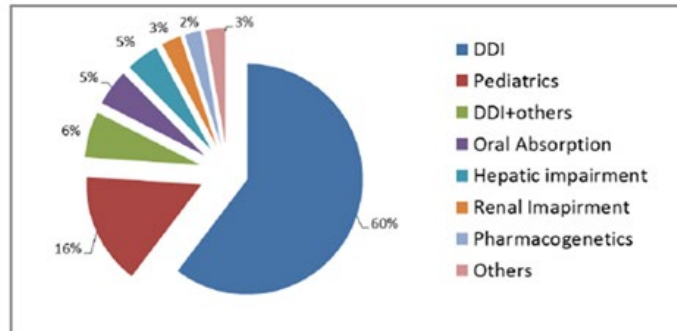
41 Labels with *in-silico* substitutes for clinical data informed by Simcyp

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

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.

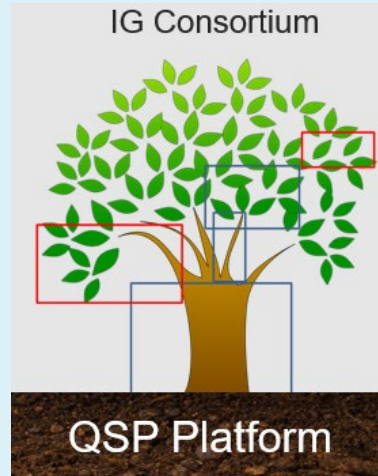
abbvie

Lilly



Bristol-Myers Squibb

IG Consortium



QSP Platform



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**.

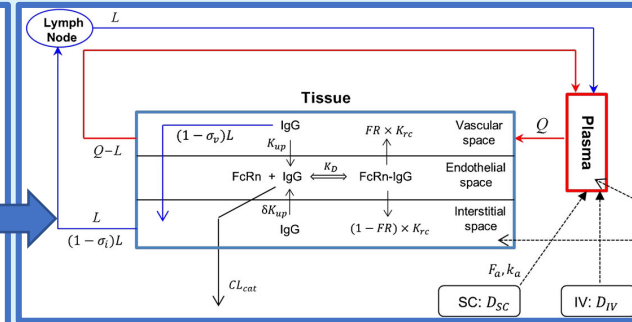
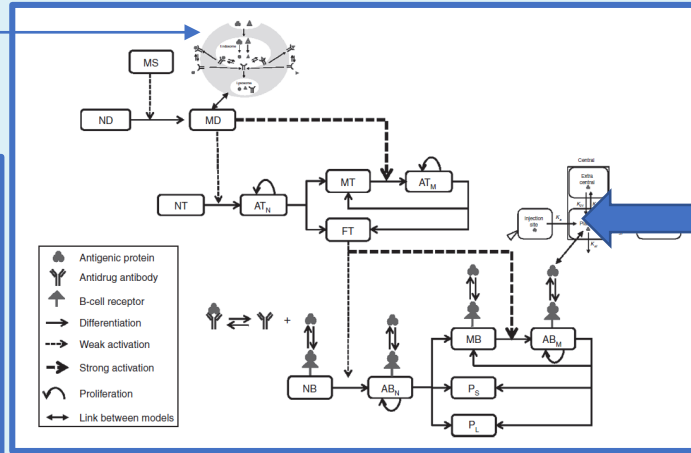
IG Model

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)

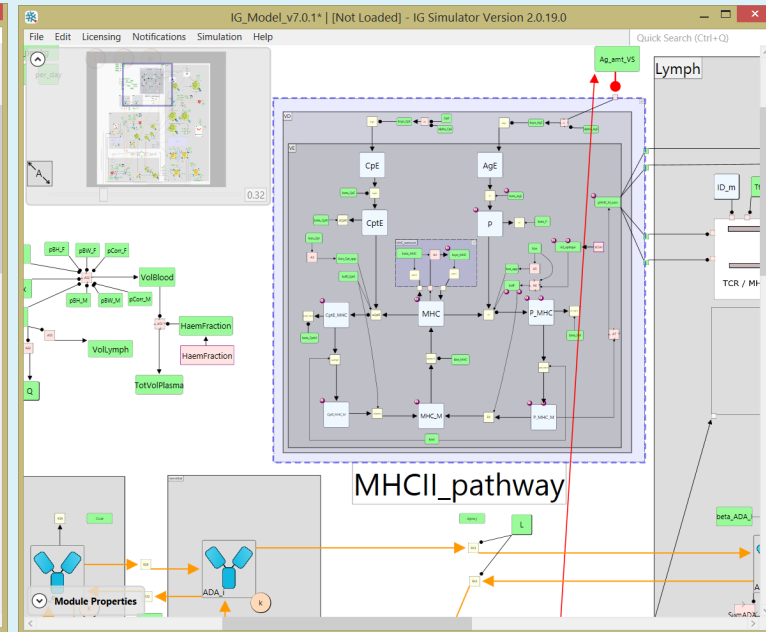
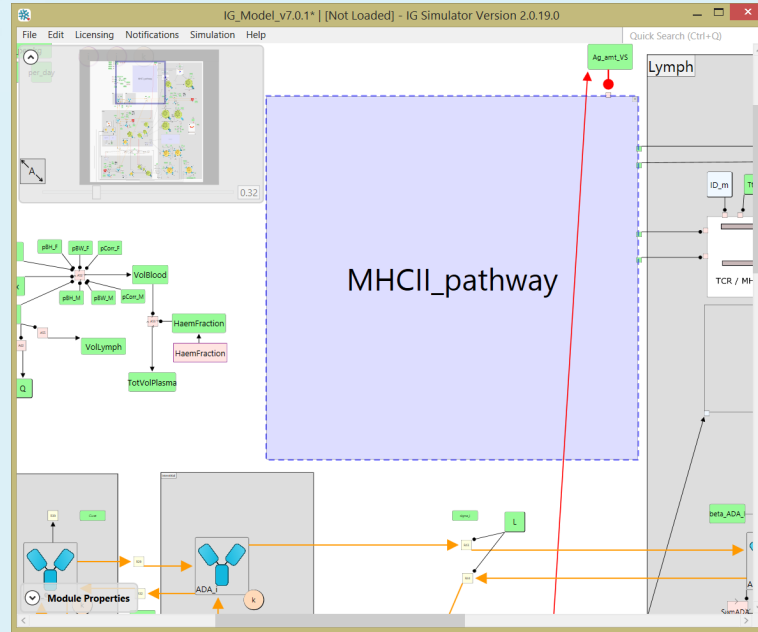
Biological scope expansion

IG Model V2 (Q1 2019)

Validation

IG Model V3 (Q1 2020)

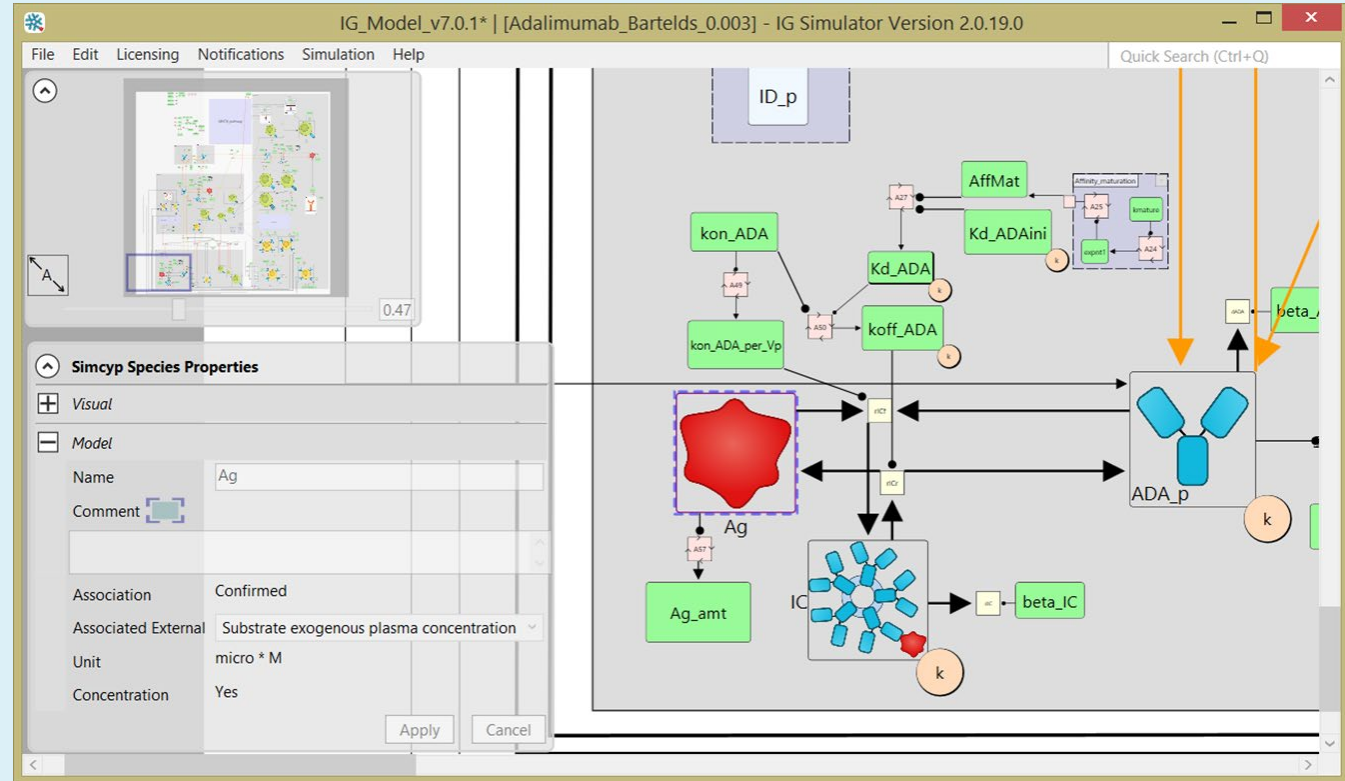
Modular Biological Process Map interface



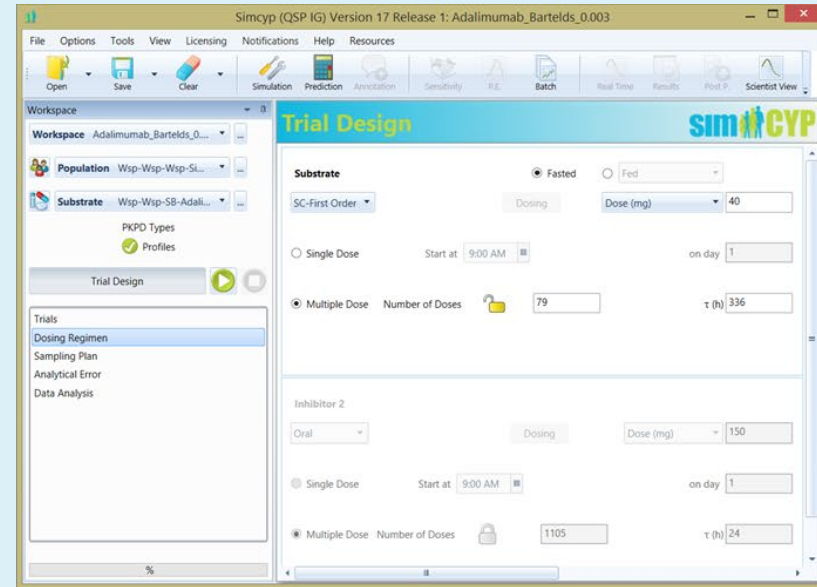
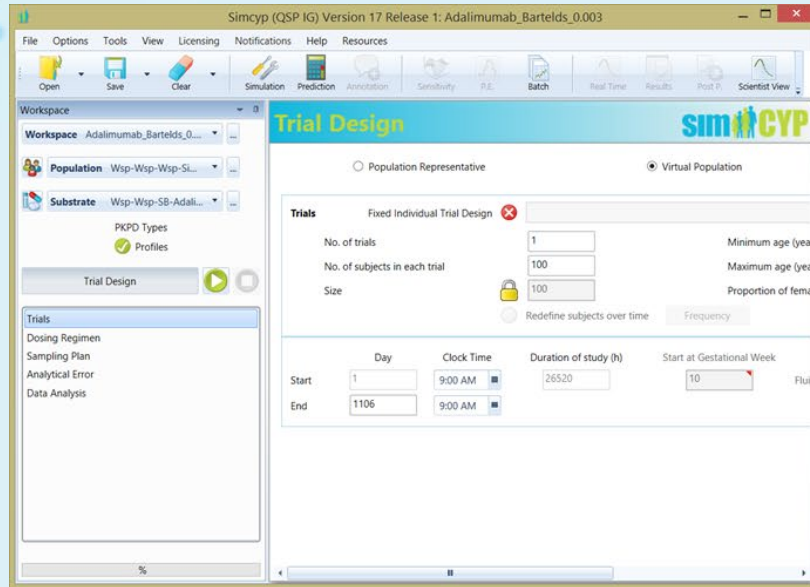
- Modules encapsulate complex mechanisms which are connected to the model through well defined interfaces.
- This facilitates both visualisation and consortium team development of multiscale mechanistic models.

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

Simcyp (QSP IG) Version 17 Release 1: Adalimumab_Bartelds_0.003

Workspace: Adalimumab_Bartel...

Population: Wsp-Wsp-Ws...

Substrate: Wsp-Wsp-SB...

PKPD Types: Profiles

Trial Design

Phys Chem and Blood Binding

Absorption

Distribution

Elimination

TMDD

Brain

MHC II Epitopes

PD Basic 1

Wsp-SB-Adalimumab

Number Of Epitopes: 2

Weak Binding Constant (nmol/L): 4000

MHC II Allele	Gene	Epitope 1 Binding Constant Unit: nmol/L	Epitope 2 Binding Constant Unit: nmol/L
> DRB1*04:01	DRB1	82	56.7
DRB1*04:03	DRB1	52.35	98.57
DRB1*04:04	DRB1	120	25.33
DRB1*04:07	DRB1	83.15	69.44
DRB1*04:11	DRB1	38.29	67.67
DRB1*07:01	DRB1	50	51.33
DRB1*08:02	DRB1	204	194.67
DRB1*08:11	DRB1	74.95	4000
DRB1*11:01	DRB1	211.33	195.33
DRB1*14:04	DRB1	35.8	4000
DRB1*15:01	DRB1	98.67	4000
Rest of DRB	DRB1	4000	4000
DQ	DQ	4000	4000
DP	DP	4000	4000

Simcyp (QSP IG) Version 17 Release 1: Adalimumab_Bartelds_0.003

Workspace: Adalimumab_Bartel...

Population: Wsp-Wsp-Ws...

Substrate: Wsp-Wsp-SB...

PKPD Types: Profiles

Trial Design

Phys Chem and Blood Binding

GI Tract

Tissue Composition

Tissue Flow Rates

Brain

Lung

Additional Organ

FcRn IgG

Lymph & Subcutaneous

Target

Blood

HLA Genotype

Immune Cell Baselines

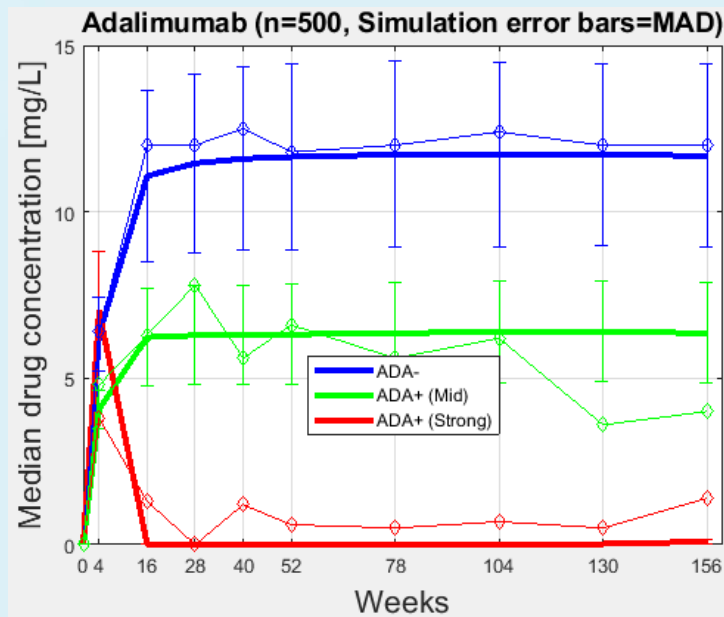
Wsp-Wsp-Sim-Healthy Volunteers.MHCII

HLA-DRB1		HLA-DQ		HLA-DP	
MHC II Allele	Allele Frequency	MHC II Allele	Allele Frequency	MHC II Allele	Allele Frequency
> DRB1*04:01	0.014302281	> DQ	1	> DP	1
DRB1*04:03	0.000386548				
DRB1*04:04	0.042520294				
DRB1*04:07	0.014302281				
DRB1*04:11	0				
DRB1*07:01	0.022419791				
DRB1*08:02	0.001159644				
DRB1*08:11	0				
DRB1*11:01	0.029377658				
DRB1*14:04	0				
DRB1*15:01	0				
Rest of DRB	0.875531503				

- 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.

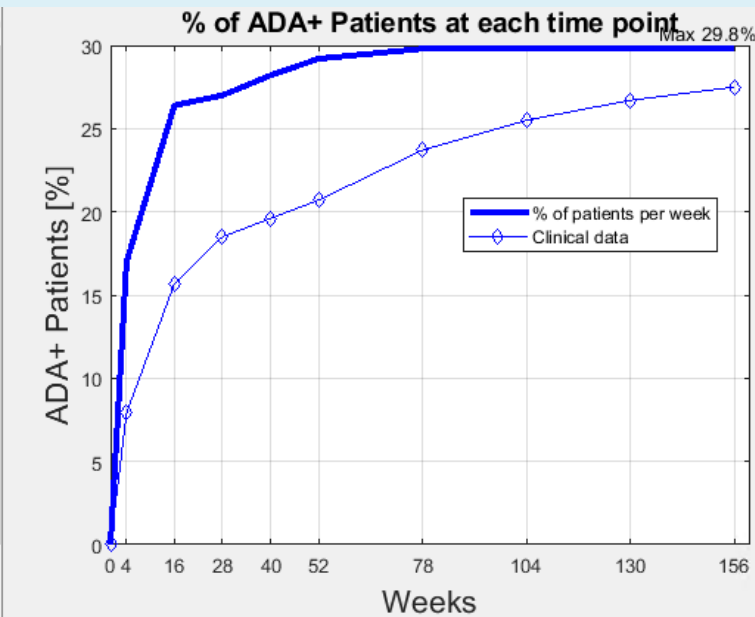
Virtual trial simulation: Adalimumab example

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



Simulation

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

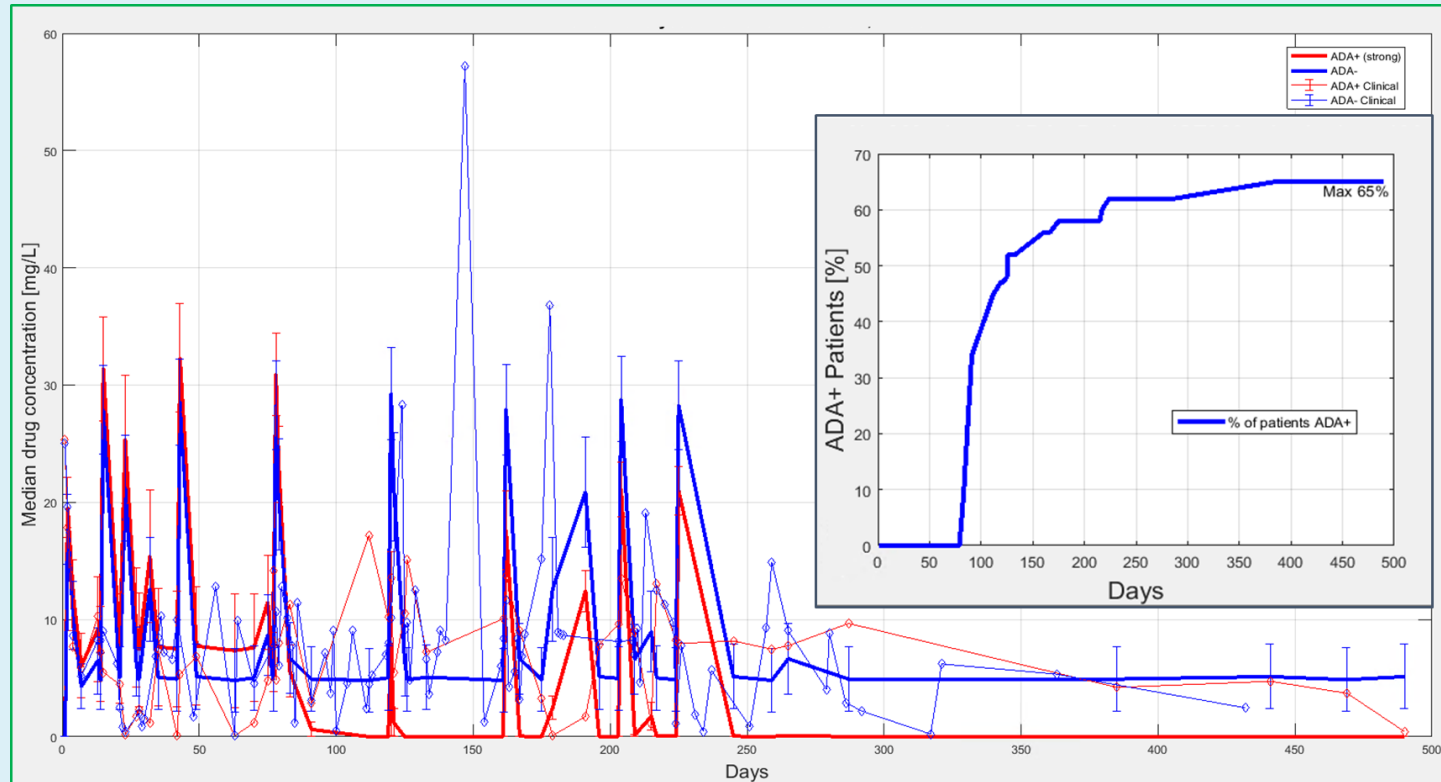


Clinical Data

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

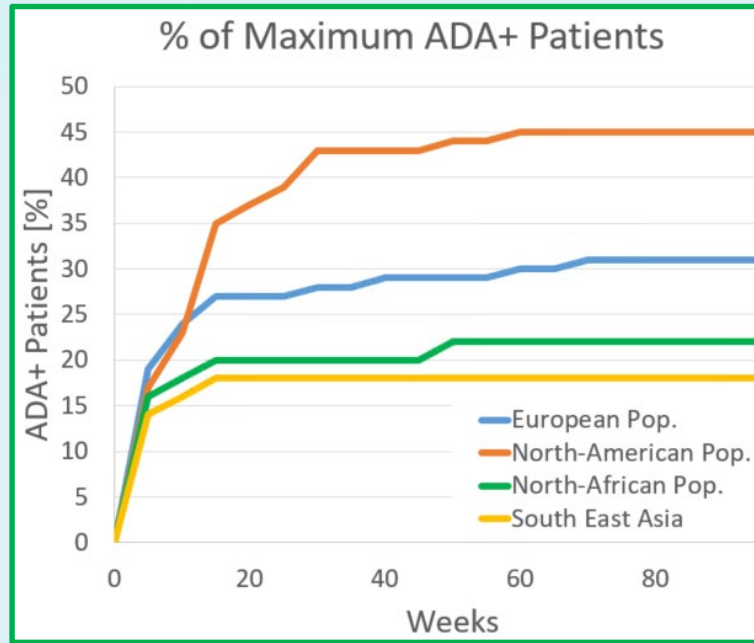
Compound X: IG does not impact PK

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

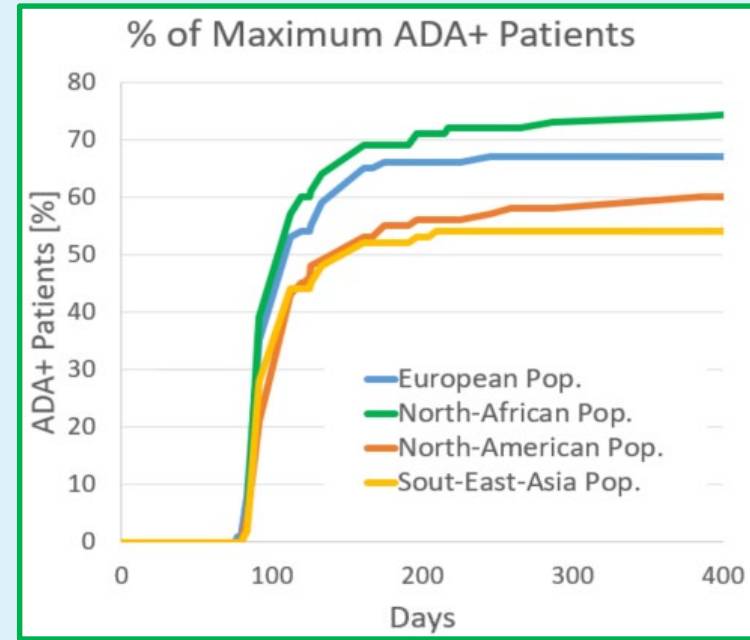


Incidence of IG in different populations.

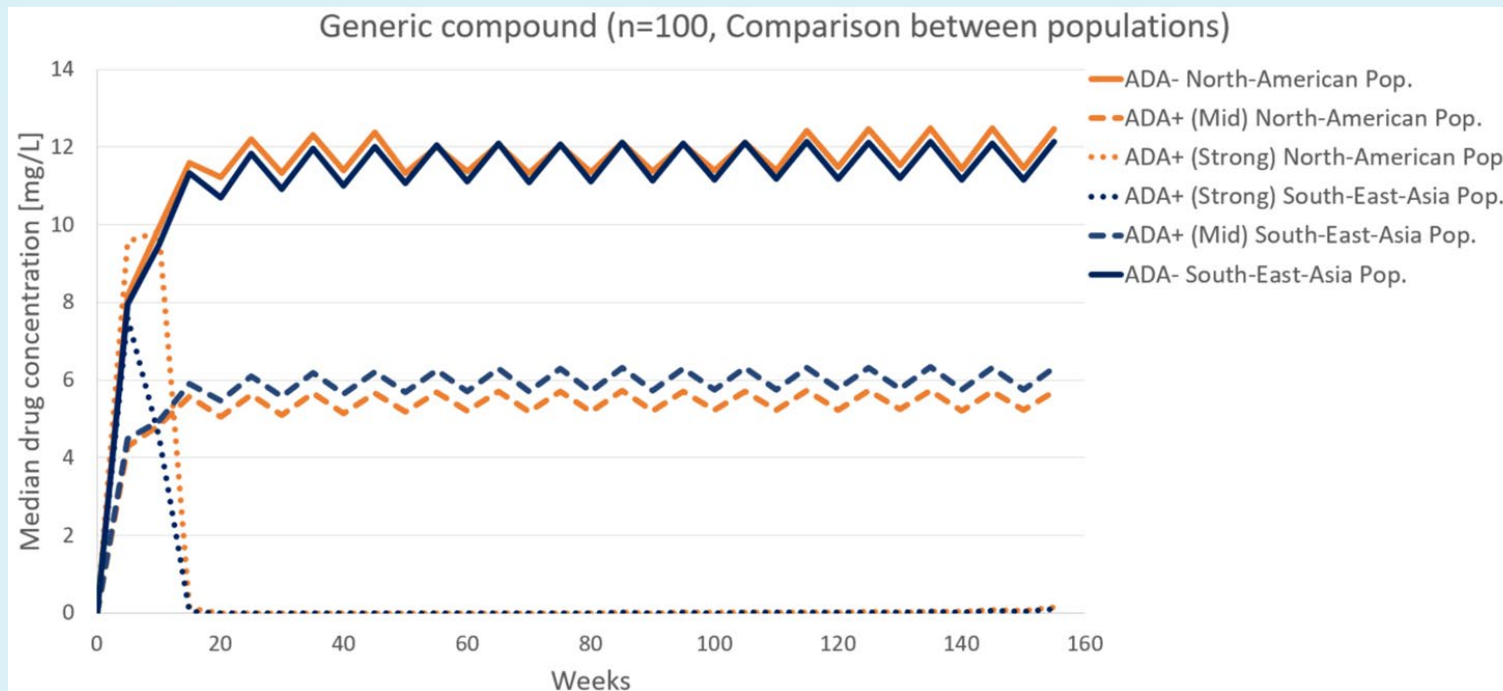
Compound X



Compound Y

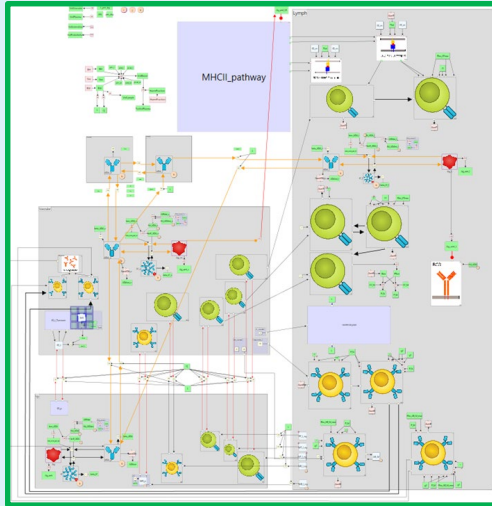


PK in different populations



Application of IG Simulator

Immune
response
model



Simcyp
BPBK

HLA Allele	Gene	Epitope 1 Binding Constant Units	Epitope 2 Binding Constant Units
DRB1*0401	DRB1	82	36.7
DRB1*0409	DRB1	52.95	98.57
DRB1*0414	DRB1	120	23.00
DRB1*0407	DRB1	81.15	18.44
DRB1*0411	DRB1	28.20	67.67
DRB1*0701	DRB1	50	51.00
DRB1*0402	DRB1	204	194.67
DRB1*0411	DRB1	74.95	4000
DRB1*1101	DRB1	211.33	193.33
DRB1*0404	DRB1	318.0	4000
DRB1*1501	DRB1	98.67	4000
Rest of DRB	DRB1	4000	4000
DO	DO	4000	4000

- 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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Neil Benson
Head of QSP Operations

IG Model



Mario Giorgi



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IG Simulator



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David Hollinshead



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