FROM MOLECULE TO PATIENT

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The Development of Consortium QSP Model of Immunogenicity with Case Examples

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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

89% incidence of immunogenicity
49% immunogenicity impact on efficacy
IG is mostly tackled preclinically:

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

*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).
“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

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.

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**

**IG Model V1 (Q1 2018)**
- Integration & IT development
- Bioinformatics (IEDB)

**IG Model V2 (Q1 2019)**
- Biological scope expansion

**IG Model V3 (Q1 2020)**
- Validation

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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)
IG Simulator

Biological Process Map interface

Simcyp simulator

Read workspace file.

Read IG Model and augment ODEs.

Export IG Model code.

Write IG Model.

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.
• 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%
• 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

 Generic compound (n=100, Comparison between populations)
Application of IG Simulator

- 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.
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Certara IG Consortium team

Leadership

- Andrzej Kierzek
  Head of Systems Modelling
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  SVP and Head of QSP
- Neil Benson
  Head of QSP Operations

IG Model

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- Maciej Swat
- Ben Small

IG Simulator

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- David Hollinshead
- Adrian Barnett