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)?

**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.
QSP: An established discipline

Journal

CPT: Pharmacometrics & Systems Pharmacology

2012

Book

Systems Pharmacology and Pharmacodynamics

2016

Networks and Communities

ASCPt
American Society for Clinical Pharmacology & Therapeutics

Systems Pharmacology (SP) Community

aaps® American Association of Pharmaceutical Scientists

SYSTEMS PHARMACOLOGY COMMUNITY

IQ
INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

CERTARA
QSP uptake by Pharma

REVIEW

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 and Mary E. Spilker.
QSP: Extrapolation

**Statistical Models**

- **PMx**
  - Dose/Concentration vs. Response
  - Question mark indicating extrapolation

- **MBMA**
  - Dose/Concentration vs. Response
  - Question marks indicating extrapolation

**Mechanistic Models**

- **QSP**
  - Dose/Concentration vs. Response
  - Question mark indicating extrapolation
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:
  o Which biomarkers do we require to achieve this?

• Can we predict human response to a novel mechanism based on preclinical data?:
  o What is the predicted human dose?
  o What is the best compound/modality?
QSP uptake by Regulators

Perspective
Quantitative Systems Pharmacology: A Regulatory Perspective on Translation

Issam Zineh

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

Diagram: Graph showing stages of hope-hype lifecycle with QSP trajectory and FDA QSP submissions.
Still some way to go: comparison with PBPK FDA submissions using PBPK modelling

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

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

Ping Zhao

QSP: Dose (regimen) prediction and Target validation?
Application of QSP in Regulatory Review: FDA

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

Manoj Khurana¹, Immo Zadezensky², Naomi Lowy³, Dragos Roman³, Jean-Marc Guettier⁴, Liang Li⁵, Jeffry Florian⁵, Chandrakas Sathijwalla⁶, Vikram Sinha⁴ and Nitin Mehrotra⁴

- Placebo
- Proposed regimen
- QSP suggested regimen
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
QSP model predictions

- **NGF mAb**: \(~1000 \times K_D\)

- **TrkA small molecule**: \(xx K_D\)

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

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 \(\sim 5-10\) mg

\(\Rightarrow\) Efficacy & dose could have been predicted from QSP model (before any clinical data were published)
the lower dose achieved was ~4 × IC50 at Cmax and dropped to ~1 × IC50 at 4 h. The differential efficacy of these two doses implies that, at least for this endpoint, an exposure that achieves a multiple of IC50 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
PKPD analysis reveals inferiority compared to SoC

Ibuprofen 600 mg ~275/20-fold IC₅₀ bound/unbound
Tanezumab proceeding to filing with a single low dose in OA only

12 August 2019

Estimated market value: anti-NGFs drug class

$11 Billion
Original drug class market estimates

$2 Billion
Revised drug class estimates

$?
Low dose and with moderate-to-severe osteoarthritis (OA)

After FDA clinical hold in 2012 which was eventually reversed in 2015. Links between NGF blockade and dangerous changes to the nervous system and joint destruction.
Target site occupancy: Emerging generalizations from clinical and preclinical studies

Sarah Grimwood a,*, Paul R. Hartig b

Efficacious concentration rule of thumb: \( \sim 3-10 \times K_i \) ?

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
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
A combined model reduction algorithm for controlled biochemical systems

<table>
<thead>
<tr>
<th>Dimension</th>
<th>EBT error</th>
<th>Lumping error</th>
<th>Stiffness</th>
<th>Combined error</th>
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<td>0.76%</td>
<td>≈ 0%*</td>
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<tr>
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<td>#</td>
<td>0.01%</td>
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<td>#</td>
<td>53.52%</td>
<td>18</td>
<td>41.10%</td>
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<tr>
<td>1</td>
<td>#</td>
<td>55.73%</td>
<td>1</td>
<td>50.46%</td>
</tr>
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</table>

[Diagram showing model reduction and output concentration over time]
QSP Big Topics

• Immunogenicity
  o Predict impact on PKPD for biologicals
  o Bio-similars

• Immuno-Oncology
  o Combination therapy: target selection and dosing schedule

• Neurodegenerative diseases
  o Target validation in Alzheimer's Disease

• Infectious Diseases
  o Resistance, vaccination

• ....
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.
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**
Case study: PCSK9

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).

<table>
<thead>
<tr>
<th>Antibody Drug</th>
<th># Binding peptides</th>
<th># MHC II alleles</th>
<th>% ADA+ Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bococizumab (Pfizer)</td>
<td>2</td>
<td>12</td>
<td>68% (Ridker, 2017)</td>
</tr>
<tr>
<td>Alirocumab (Regeneron)</td>
<td>1</td>
<td>1</td>
<td>5.1% (Roth, 2017)</td>
</tr>
<tr>
<td>Evolocumab (Amgen)</td>
<td>0</td>
<td>0</td>
<td>0.1% (Henry, 2016)</td>
</tr>
<tr>
<td>GNE anti-PCS9 (Genentech)</td>
<td>2</td>
<td>8</td>
<td>4% (GENE data*)</td>
</tr>
</tbody>
</table>

*Based on Phase II clinical study with ~200 subjects.
IG is highly **variable**

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

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Frequency of ADAb formation, % (no. of studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RA</td>
</tr>
<tr>
<td>ABA</td>
<td>2–20 (7)</td>
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<tr>
<td>ADA</td>
<td>0–51 (33)</td>
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<tr>
<td>CZP</td>
<td>2.8–37 (7)</td>
</tr>
<tr>
<td>ETN</td>
<td>0–13 (25)</td>
</tr>
<tr>
<td>GLM</td>
<td>2–10 (11)</td>
</tr>
<tr>
<td>INF</td>
<td>8–62 (48)</td>
</tr>
<tr>
<td>RTX</td>
<td>0–21 (8)</td>
</tr>
<tr>
<td>SEC</td>
<td>0–16 (14)</td>
</tr>
<tr>
<td>TCZ</td>
<td>8–11 (3)</td>
</tr>
<tr>
<td>CT-P13</td>
<td>26–52 (2)</td>
</tr>
</tbody>
</table>

- **Compound**
- **Dose and administration**
- **Patient population**
- **Disease state**
- **Co-medications**
- **Other**
“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.”
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).
Overview of IG Simulator

Biological Process Map interface

- Read workspace file.
- Write IG Model
- Read IG Model and augment ODEs
- Export IG Model code.

Simcyp simulator

- Simulate virtual trial and output results.

IG Model code and documentation

Matlab code
R code
R code with equation in C
Excel file with documentation of variables, equations and parameters

IG Model code and PBPK variable connections in Lua

Virtual trial results in Simcyp formatted Excel file
Example: Adalimumab

**ADA response**

- % of Maximum ADA+ Patients (Bartelds criterion)
  - Max 21.2%

**Pharmacokinetics**

- Adalimumab analysed with Bartelds criterion (n=500)

**ADA+ Cohort**
- ADA+ 12-100AU/ml
- Strong ADA+ >100AU/ml

**Model**
- 60%
- 40%

**Data**
- 59%
- 41%

*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.

**Immunogenicity is highly variable.** Different compounds exhibit large differences in ADA incidence in different populations.
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.
A Model-Based Approach to Quantify the Time-Course of Anti-Drug Antibodies for Therapeutic Proteins

Yupeng Ren¹, Liang Li², Susan Kirshner³, Yaning Wang³, Chandrahas Sahajwalla¹ and Ping Ji¹,*

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.

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

Osman N. Yogurtun¹, Zubin E. Sauna³, Joseph R. McGill², Million A. Tegenge¹, and Hong Yang¹,*

We validated TCPot using an experimental immunogenicity dataset, making predictions on the population-based immunogenicity risk of 15 protein-based biotherapeutics. Immunogenicity rankings generated using TCPot are consistent with the reported clinical experience with these therapeutics.
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. Lei,5 and Craig J. Thalhauser5,6

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.
QSP Conference 2020: Leiden, The Netherlands

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Quantitative Systems Pharmacology Conference 2020
April 22-24, 2020
Leiden, The Netherlands
www.qspc.eu

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The Netherlands
Stadsgehoorzaal

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