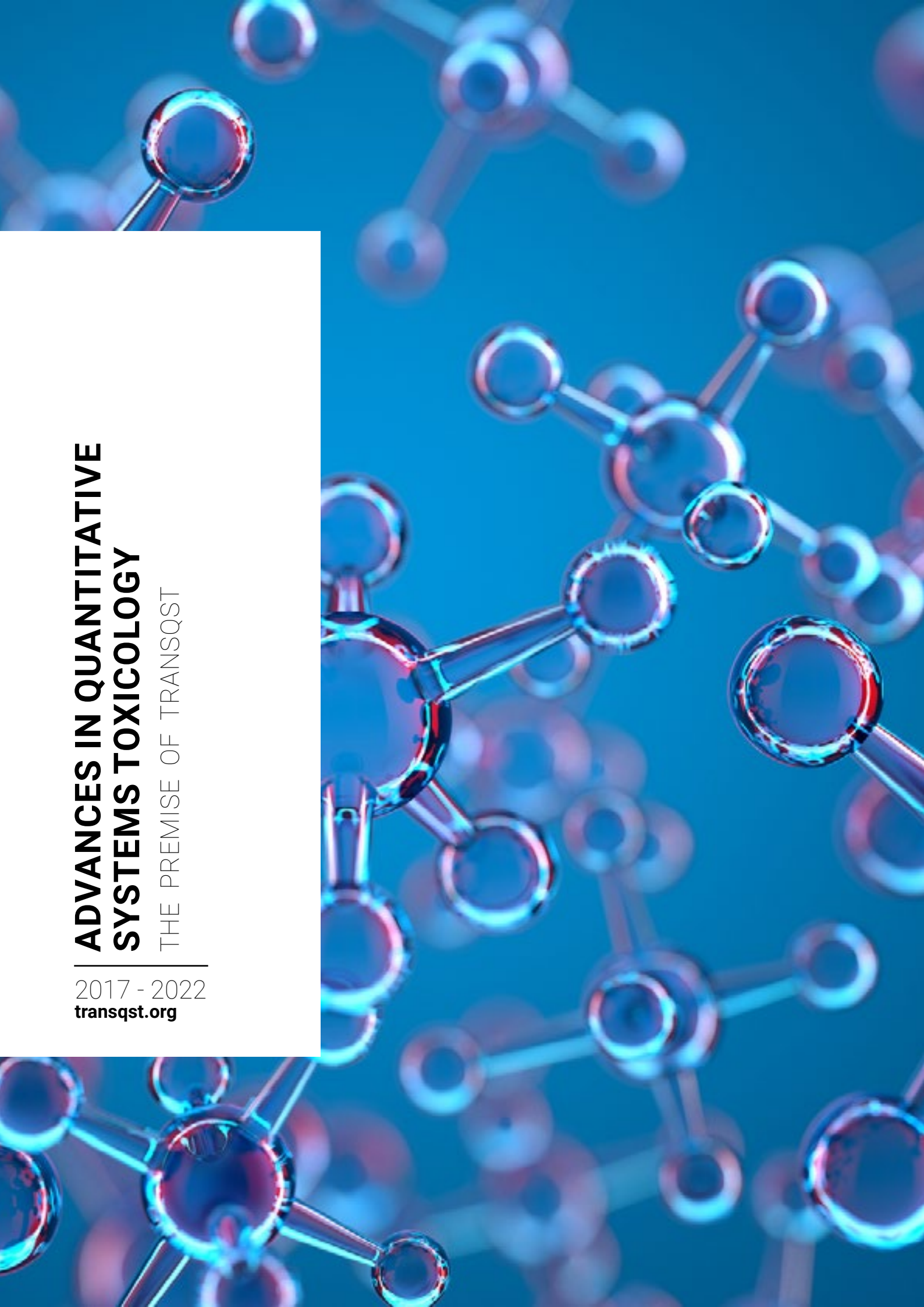

ADVANCES IN QUANTITATIVE SYSTEMS TOXICOLOGY

THE PREMISE OF TRANSQST

2017 - 2022

transqst.org

TransQST Overview

TransQST - Translational quantitative systems toxicology to improve the understanding of the safety of medicines.

23 partners
18 Mill €
68 months

01.01.2017 · 31.08.2022

List of partners

ULIV
University of Liverpool - United Kingdom **(Project Coordinator)**

UL
Universiteit Leiden - Netherlands

IMIM
Fundació Institut Hospital del Mar d'Investigacions Mèdiques (IMIM) - Spain

SYNAPSE
Synapse Research Management Partners SL - Spain

UM
Universiteit Maastricht - Netherlands

EMBL
European Molecular Biology Laboratory - Germany

UOXF
The Chancellor, Master and Scholars of the University of Oxford - United Kingdom

CERTARA:
Certara UK Limited - United Kingdom

UNIVIE
Universität Wien - Austria

IFADO
Forschungsgesellschaft für Arbeitsphysiologie und Arbeitsschutz e.V - Germany

CROWNBIO
Crown Bioscience Netherlands BV - Netherlands

EMC
Erasmus Universitair Medisch Centrum Rotterdam - Netherlands

ABBVIE
AbbVie Deutschland GmbH & Co. KG - Germany (Project Lead)

ELI-LILLY
Eli Lilly and Company Ltd - United Kingdom

SARD
Sanofi Recherche & Développement - France

AZ
AstraZeneca AB - Sweden

GSK
GSK PLC - United Kingdom

IRIS
Institut de Recherches Internationales Servier - France

JANSSEN
Janssen Pharmaceutica NV - Belgium

ORION
Orion Corporation - Finland

BI
Boehringer Ingelheim GmbH - Germany

UKHD
Universitaetsklinikum Heidelberg - Germany

VERTEX
Vertex Pharmaceuticals (Europe) Limited - United Kingdom

Acknowledgement:

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 116030. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA (European Federation of Pharmaceutical Industries & Associations).

Table of Contents

KEYNOTE

Keynote

TransQST was conceived as a response to the need to accelerate and optimize the development process for new molecules, contributing to the delivery of safer and faster drugs.

Despite much progress being made in recent years, the development of medicines remains an extremely lengthy and costly process, with a low success rate. Bringing a new drug to market takes between 10 to 15 years[1] and around 1 billion US dollars[2]. Despite this huge investment both in terms of time and money and the fact that clinical trials are designed based on sound results from preclinical testing, a considerable number of drug candidates fail during the clinical research phase. Currently, only 10% of all drug candidates[3] make it through the development pipeline and reach the market.

TransQST (http://transqst.org) is a public-private partnership part of the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) scheme[4], funded by the European Union's Horizon 2020 research and innovation programme and EFPIA[5]. The project was conceived as a response to the urgent need to accelerate and optimize the development process for new molecules, with the final goal to contribute to the delivery of safer and faster drugs, translating to a direct health benefit to society.

The consortium was launched on 1st of January 2017, spanning until 31st of August 2022, with the involvement of ten first-tier pharma partners and thirteen academic partners[6] comprising top universities, research centres, hospitals, and small and medium-sized enterprises.

Our overarching aim was to demonstrate that quantitative and systems approaches in pharmacology and toxicology can be practically applied in drug research and development and used to enhance decision making[7]. To achieve this aim, the project focused on four organs as the most common targets for drug-induced injury: liver, kidney, heart, and gastrointestinal-immune system.

Currently, toxicity assessment in drug R&D relies mainly on in *vitro* and animal studies conducted at early stages of drug development (aka preclinical studies). The objective of toxicity assessment at preclinical stages is to identify potential safety concerns in human before a candidate proceeds to the clinical stage. To challenge the current practice, TransQST developed Quantitative Systems Toxicology (QST) tools and models to enable the approach as a way to improve how toxicity assessment is performed, with an emphasis in the translational capacity of models. One of our main objectives was to embed QST as a routine part of preclinical safety assessment at pharma, using QST models to

1 https://www.nature.com/articles/d41573-021-00190-9
2 https://jamanetwork.com/journals/jamafullarticle/2762311
3 https://www.nature.com/articles/nrd.2016.136
4 https://www.imi.europa.eu/
5 https://www.efpia.eu/
6 https://transqst.org/consortium/partners/
7 https://pubs.acs.org/doi/10.1021/acschemrestox.9b00499

The public-private collaboration has constituted one of the project strengths, moving forward innovative modelling approaches and illustrating their use in toxicity and safety pharmacology studies.

integrate *in vitro, in vivo and in silico* data to identify safety concerns earlier, elucidate mechanisms of toxicity and therefore, reduce attrition rates. In this scenario, QST modelling and simulation could be used to add weight of evidence and provide quantitative predictions of drug toxicity , improve our ability to translate observations from preclinical-clinical species to clinical liability and improve our confidence in determining therapeutic index. Moreover, QST models can also contribute to a 3Rs strategy helping to reduce, refine, and ultimately replace the use of animals in preclinical safety assessment.

TransQST has been successful in developing an extensive suite of models and tools, which are currently being tested by the project pharma partners for their inclusion as part of the preclinical safety assessment. A real-life example of how TransQST models can have a clear impact on pharma drug development decisions was presented with a COVID-19 modelling and simulation study performed by the project. The team involved in cardiac modelling presented a study exploring the potential cardiac arrhythmia risk from the off-label use of chloroquine and hydroxychloroquine. These drugs, traditionally used to treat malaria and rheumatological disorders, were initially suggested as beneficial for the prevention and treatment of patients with COVID-19 due to SARS-CoV-2 infection but are associated with electrocardiographic and cardiotoxic effects. The TransQST study demonstrated the increased proarrhythmia risk of the proposed treatment, illustrating how QST models can be used to make real-life risk assessments[8].

The public-private collaboration has constituted one of the project strengths, creating a multi-disciplinary working space to develop advanced mathematical, computational, and biological modelling solutions, moving forward innovative modelling approaches for different organ toxicities, which illustrate how quantitative models can successfully be used in toxicity and safety pharmacology studies. However, this perfect interplay of experts, which has allowed the project to leverage knowledge from different fields within academia and industry, is a result of several years of collaborative work. Much dedication was needed for specialists coming from different areas to reach mutual understanding and develop a so called “TransQST Esperanto” born through trial and error and constant dialogue. This experience

8 https://pubmed.ncbi.nlm.nih.gov/33620150/

has evidenced the need for a new generation of experts with multidisciplinary knowledge and skills. Training scientists in complementary fields, such as toxicology and computational modelling, would help to better leverage novel techniques and approaches available today, speeding-up from bench to bedside translations.

The experience of QST modelling in areas such as heart and liver demonstrate that this is a long-term endeavour. However, in the close to six years of project duration, TransQST has managed to enhance their application within an industrial context to improve mechanistic understanding and prediction of safety liabilities of new drug candidates at early stages of the drug development pipeline. Although there is still a long way to go until a more widespread application and acceptance of modelling and simulation in toxicology and safety pharmacology can be reached within the pharma industry, regulatory agencies, and even further until it is fully embraced as routine part of drug discovery and development pipelines, we are proud to conclude that TransQST has ensured another step has been taken in the direction of removing scepticism around modelling and simulation in drug safety assessment, and in increasing its credibility. Developing in silico strategies to understand the risk of drug toxicity in humans is a crucial step towards a faster development of more effective drugs and being able to replace preclinical toxicity testing of candidate molecules in animals.

This booklet aims to provide a comprehensive summary of the project results as of January 2023, after close to six years of fruitful collaboration. We hope you enjoy reading it and that the outcomes of TransQST may provide insights for future projects and serve to inspire further collaborations in the field of systems toxicology.

Sincerely,
TransQST Executive Committee members.

Christopher Goldring
Project Coordinator, ULIV

Loic Laplanche
Project Industry Lead, AbbVie

Derek Leishman
Eli-Lilly

Sean Turner
AbbVie

Inari Soininen
Synapse

FRAMEWORK

for model validation

FRAMEWORK
for model validation

What best characterizes the XXI century is the excess of data. In many cases the society and actors are incapable of harnessing and making the most of the enormous amounts of data available. To derive knowledge requires efficient ways to collect and interrogate this input and use it to inform better decision making. As integrated repositories of data and current understanding, QST models help to accomplish this goal.

Therefore, the overarching aim behind the models developed and enhanced in TransQST can be considered twofold. On the one hand, they can make use of the substantial amounts of data available to better predict clinical outcomes in response to new drugs. On the other hand, these models can also play a significant role within the drug development workflow to improve experimental designs. This way, they are also subject to contributing to the 3Rs (replace, reduce, and refine) framework and reducing the use of animals in research.

Model validation is one of the key aspects of a successful model development process and a requisite for their adoption as part of the industry practice. Based on the traditional 3Rs approach, the consortium designed an aspirational framework for the validation of TransQST models, extending it to 5Rs: Replace, Reduce, Refine, Reproduce and Reveal. Using this aspirational framework, the consortium designed a pipeline for model validation, where Replace means replacing the need for animal experimentation, Reduce can be seen as reduction in terms of attrition or time, Refine seen as better decision making based on the information provided by the models, Reproduce as the importance of results reproducibility in science, and finally Reveal as revealing mechanistic details and progressing mechanism-based risk assessment and decision making.

The following chart summarizes said model validation framework:

R1

Replace:
How QST models and tools replace the need for animal experiments?

R2

Reduce:
How QST models and tools reduce time, attrition rate?

R3

Refine:
How QST models refine decision making?

R4

Reproducibility:
Do QST models and tools produce consistent/reproducible results and predictions?

R5

Reveal:
Do QST models and tools reveal mechanism of toxicity?

SUMMARY

of project results

SUMMARY
of project results

TransQST has carried out significant efforts in data curation, integration, and annotation as well as developed and enhanced a broad panel of tools used to identify and quantify toxic mechanisms. In addition, new in vitro and in vivo data sets designed specifically for the building and validation of the models developed within the project have been generated.

To progress drug safety predictions in liver, kidney, heart and gastro-intestinal immune system, the consortium has both developed new TransQST models and enhanced pre-existing models aimed at assessing different organ toxicities. Among these we can find novel systems models, using ordinary differential equation (ODE) and agent-based (ABM) approaches, coupled with more established modelling approaches such as physiologically-based pharmacokinetic (PBPK) models. Additionally, TransQST models have been assessed by internal users and the modelling teams according to technology readiness levels (TRLs) as a type of measurement system used to assess the maturity level of a particular technology (see Figure 1).

Following the project´s open-access philosophy, these outputs have been made freely accessible through public repositories as far as possible and will therefore serve to support other initiatives and the wider scientific community beyond TransQST. The results can be easily accessed through our website:

https://transqst.org/results/

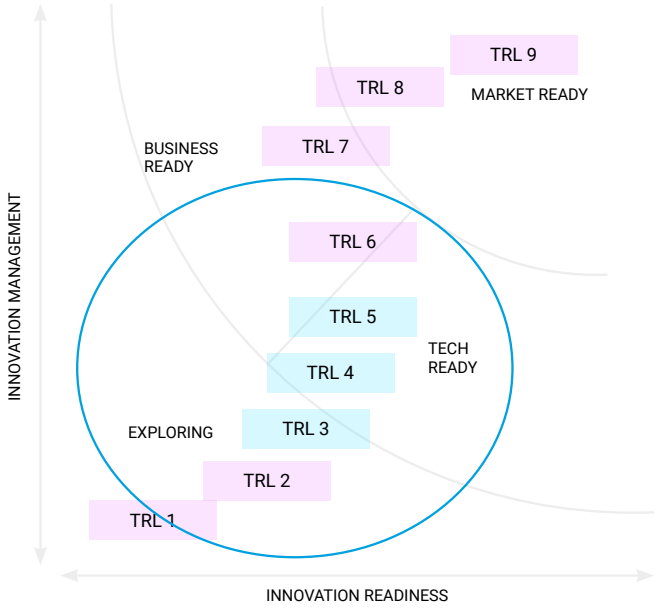

Figure 1. TRLs (technology readiness levels) are a type of measurement system used to assess the maturity level of a particular technology: TRL 1 – basic principles observed; TRL 2 – technology concept formulated; TRL 3 – experimental proof of concept; TRL 4 – technology validated in lab; TRL 5 – technology validated in relevant environment (industrially relevant environment in the case of key enabling technologies); TRL 6 – technology demonstrated in relevant environment (industrially relevant environment in the case of key enabling technologies); TRL 7 – system prototype demonstration in operational environment; TRL 8 – system complete and qualified; TRL 9 – actual system proven in operational environment (competitive manufacturing in the case of key enabling technologies; or in space).

PROJECT RESULTS · JANUARY 2023

22 models

11 tools

100 GB
of curated/generated data

70 publications

Multiscale or Systems Models:

Model	Created in TransQST	Accessibility	Available ate	TRL	Further information
Purkinje fibre model - UOXF	Yes	Public	Virtual Assay (free for academics) and CellML	5	PMID: 32251669
Tor-ORd model - UOXF	Enhanced	Public	Virtual Assay, CellML, and GitHub: https://github.com/jtmff/torord	5	PMID: 31868580
Tor-ORd model with contractility included - UOXF	Enhanced	Public	Virtual Assay (free for academics) & CellML	5	PMID: 32710902
Hemodynamic cardiovascular systems modelling framework - UL	Yes	Public	https://github.com/vanhasselt-lab/hemodynamic-simulator https://hemosim.lacdr.leidenuniv.nl/	5	PMID: 35213797

Model	Created in TransQST	Accessibility	Available ate	TRL	Further information
GSMN model for drug-induced liver injury (DILI) - Certara	Yes	Public	https://www.ebi.ac.uk/biomodels/MODEL2111050001	3	PMID: 28782239
Steatosis model - Certara	Yes	Public	Available via publication materials	3	PMID: 29921957
Reactive metabolite model - Certara	Yes	Public	Available via publication	3	PMID: 19371757
Logic-based dynamic modelling framework to model drug induced liver injury - UKHD, UL	Yes	Public	https://www.ebi.ac.uk/biomodels/MODEL2206070001 https://github.com/saezlab/LogicODE_GFP_SR	3	PMID: 33957093
Prototype feedback model for liver injury/regeneration - Eli-Lilly, UL, Certara	Yes	Consortium	Early prototype, reconstructed based on original article. Code available upon request	2	PMID: 22395210

Model	Created in TransQST	Accessibility	Available ate	TRL	Further information
Translational QST model for Drug-Induced Kidney Injury (DIKI) - AbbVie, Certara, UL	Yes	Public	www.ebi.ac.uk/biomodels/MODEL2204290001	2	

Model	Created in TransQST	Accessibility	Available ate	TRL	Further information
Multi-scale epithelial GI model (ODE) - AZ	Yes	Public	www.ebi.ac.uk/biomodels/MODEL2212120003	5-6	
Multi-scale GI epithelial model (ABM) - AZ	Yes	Public	www.ebi.ac.uk/biomodels/MODEL2212120002	5-6	
Drug-induced gastrointestinal acute inflammation modelling framework - BI, Janssen	Yes	Consortium	Internal model repository BI Nonclinical Drug Safety-US department and TransQST SharePoint	4	
Modified Shankaran 2017 model - GSK, AZ et al.	Yes	Consortium	No - publishing the model TBD	3	Original Shankaran model published PMID: 28941225

Figure 2. Multiscale / systems models developed or enhanced in TransQST. Accessibility refers to models being released for public use or for internal use of TransQST consortium members.

Physiologically Based Pharmacokinetic (PBPK) Models:

Model	Created in TransQST	Accessibility	Available ate	TRL	Further information
Cardiac PBPK permeability - limited model - Certara	Yes	Public	https://github.com/jszlek/CardiacPBPK https://sourceforge.net/projects/cardiacpbpk/	5	

Model	Created in TransQST	Accessibility	Available ate	TRL	Further information
Human APAP PBPK model - Certara	Yes	Public	Simcyp Simulator: www.certara.com/software/simcyp-pbpk/	3	Precursor model in BioModels: www.ebi.ac.uk/biomodels/BIOMD0000000609
Rat APAP PBPK model - Certara	Yes	Consortium	Simcyp Simulator: www.certara.com/software/simcyp-pbpk/	3	Precursor model in BioModels: www.ebi.ac.uk/biomodels/BIOMD0000000609
Mouse APAP PBPK model - Certara	Yes	Consortium	Simcyp Simulator: www.certara.com/software/simcyp-pbpk/	3	Precursor model in BioModels: www.ebi.ac.uk/biomodels/BIOMD0000000609

Model	Created in TransQST	Accessibility	Available ate	TRL	Further information
PBPK model cisplatin - Certara	Enhanced	Consortium	Model in QSP format at Certara. Plan to be published as part of kidney QST model.	3	PMID: 3051521
PBPK model carboplatin - Certara	Enhanced	Consortium	Model in QSP format at Certara. Plan to be published as part of kidney QST model.	3	PMID: 3051521
Human PBPK model cyclosporine A - Certara	Enhanced	Consortium	Model in Simcyp Simulator V19.	3	Earlier v. (V14) of compound use published: PMID: 32055591
Rat PBPK model cyclosporine A - Certara	Enhanced	Consortium	N/A.	3	

Figure 3. Physiologically Based Pharmacokinetic (PBPK) Models developed or enhanced in TransQST. Accessibility refers to models being released for public use or for internal use of TransQST consortium members

Project tools:

TOOL	CREATED IN TRANSQST	AVAILABILITY
TXG-MAPr	Yes	Consortium partners: https://txg-mapr.eu https://bio.tools/TXG-MAPr
iPath	Yes	Public: https://bio.tools/ipath_IMIM http://sbi.imim.es/data/ipath.tgz
Path4drug	Yes	Public: https://bio.tools/Path4Drug https://kni.me/s/7jbMNHvalhE2ZCtU
CARNIVAL	Yes	Public: https://bio.tools/CARNIVAL https://github.com/saezlab/CARNIVAL https://bioconductor.org/packages/release/bioc/html/CARNIVAL.html
Biomodels Parameters	Yes	Public: https://bio.tools/biomodels-parameter https://www.ebi.ac.uk/biomodels/parameterSearch
Biomodels Database	Enhanced	Public: https://bio.tools/biomodels https://www.ebi.ac.uk/biomodels/
DisGeNET	Enhanced	Public: https://bio.tools/disgenet https://www.disgenet.org/ https://www.disgenetplus.com
COSMOS	Enhanced	Public: https://bio.tools/cosmos-omics https://saezlab.github.io/cosmosR https://bioconductor.org/packages/release/bioc/html/cosmosR.html
CellNOpt Toolbox	Enhanced	Public: https://bio.tools/cellnoptr http://bioconductor.org/packages/release/bioc/html/CellNOptR.html
OmniPath	Enhanced	Public: https://bio.tools/OmniPath https://omnipathdb.org/
Virtual Assay Drug Screening	Enhanced	Public to academia / For fee to private entities: https://bio.tools/virtual_assay https://www.cs.ox.ac.uk/ccs/virtual-assay/

Figure 4. Tools that help to decipher and quantify toxic mechanisms developed or enhanced in TransQST. All tools have been made available through the bio.tools platform.

TransQST Models

As a result of TransQST, which had the aim of improving QST modelling and accelerating the adoption of prediction through modelling and simulation as a standard practice in the pharma industry decision-making processes, a variety of mathematical, computational, and biological modelling solutions have been developed in the project for liver, kidney, heart, and gastro-intestinal immune system. Some of these models were developed during the project life, while others were pre-existing and have been enhanced by the consortium members to the benefit of the wider scientific community.

These models consist of systems toxicology models, expressed using ordinary differential equation (ODE) or agent-based models (ABM), as well as physiological-based pharmacokinetic (PBPK) models, which in many cases have been the basis for the development of the more comprehensive QST approach developed in TransQST.

One of our main goals has been to improve QST modelling and incorporate prediction through models as a standard practice in the pharma industry decision-making processes.

Liver models
TransQST Work Package 5

Systems models

GSMN model for drug-induced liver injury (DILI)

Description:

This tutorial demonstrates two examples where physiologically based pharmacokinetic (PBPK) models were linked to two classes of systems biology models relevant to hepatocyte metabolism: Genome Scale Metabolic Networks (GSMN) and quantitative dynamic models of Gene Regulation Networks (GRNs). This revealed the utility of such linked systems models to identify network reactions that influence downstream effects of exposure, such as GSH production. This supports hypothesising particular target interactions that may have pharmaceutical or toxic effects. Incorporating GRN (Gene Regulation Networks) to PBPK supported exploring effects of stress on metabolism and by extension compound kinetics.

Partners involved:
Certara UK Limited (Certara)

Available at BioModels platform:
https://www.ebi.ac.uk/biomodels/MODEL2111050001

and published as a tutorial in:
https://ascpt.onlinelibrary.wiley.com/doi/10.1002/psp4.12230
Related software and code provided in supplementary material.

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Ciarán Fisher: ciaran.p.fisher@gsk.com

Steatosis model

Description:

Valproic acid (VPA) is associated with hepatic steatosis that needs careful management and dosing. Certain populations with comorbidities may be in higher risk of hepatotoxicity, such as those with morbid obesity and non-alcoholic fatty liver disease. To explore this, a multi-scale model linking a physiologically based pharmacokinetic (PBPK) model for valproic acid and a detailed liver metabolism model (Berndt et al., 2018) was developed to investigate drug effect on hepatic lipid metabolism. We identify that chronic treatment with VPA results in a persistent disruption in metabolites involved in lipid metabolism and higher potential for obese populations to present VPA induced hepatic steatosis. This work exemplifies the potential of QST modelling to inform translational safety across patient populations.

Partners involved:
Certara UK Limited (Certara)

Available at:
Published in:
https://www.nature.com/articles/s41467-018-04720-9

All data and public data sources used for the development, calibration, and exemplary model simulations are contained in the supplementary information. An executable SBML file of the model is available from the authors on request.

Contact:
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Prototype feedback model for liver injury/regeneration

Description:

A preliminary model adapting gene expression to liver injury and repair. Liver is a common target for drug toxicity; in response to injury, an adaptive response may be triggered to counter the effects of hepatocyte loss to maintain liver function. Such considerations were incorporated to describe dynamical changes in liver biomarkers from injury, specifically injury from ischaemic reperfusion and from partial hepatectomy. These two surgical models were chosen to simplify the initial modelling exercise, since the need to model pharmacokinetics was obviated by the “point in time” nature of these surgical models. Having explored various approaches using “toy models”, we adapted a nonlinear dynamic model (DeGracia et al. PMID: 22395210) to elucidate the interplay of hepatocellular injury and repair processes using data from the surgical models. Weighted gene correlation network analysis (WGCNA) data from rat liver after liver ischaemia that indicate changes in gene module expression were useful to parameterise the damage and regeneration responses. Specifically, module 20 reflecting DNA replication and module 210 reflecting invasion of neutrophils were used to parameterise the DeGracia-based model to describe effects of liver ischaemic reperfusion in rat. Simulations with the fitted model parameters were able to recover the observed biomarker data profiles (ALT, AST, total bilirubin). Verifying against biomarker data (ALT and Ki67), model simulations captured the injury and recovery kinetics with model parameters derived from gene networks. This preliminary case study demonstrates how modelling can link modular gene expression with liver injury outcomes. Further work will explore alternative module combinations to best derive model parameters and incorporate the pharmacokinetics of hepatotoxic drugs.

Partners involved:
Eli Lilly and Company Ltd (Eli-Lilly), University of Leiden (UL), Certara UK Limited (Certara)

Available at:
Early prototype reconstructed based on original publication below. Further development of the model is continued under the Horizon 2020 RISK-HUNT3R project.

Contact:
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James Stevens: jls.paradoxfound@gmail.com
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Ciaran Fisher: ciaran.p.fisher@gsk.com

For further details, see:
https://journals.sagepub.com/doi/10.1038/jcbfm.2012.10

Reactive metabolite model

Description:

In response to xenobiotic induced injury, including drug induced injury, compensative pathways are activated in the cell to reduce the intensity of the insult and promote regeneration. Such feedback and feedforward mechanisms from the Nrf2 response have been described in an ordinary differential equation-based model by Zhang et al. (2009). This model was adapted to identify potential species differences between mouse and rat that give rise to rat presenting higher robustness to paracetamol induced hepatotoxicity. Parameterising the reactive metabolite model to recover observed glutathione levels in untreated rat and mouse, two potential mechanisms were identified: higher reactive oxygen species production or higher Nrf2 sensitivity to reactive oxygen species in rat than mouse. This may allow the healthy rat physiology to be more primed and hence more robust against paracetamol. This work outlines the utility of QST models to guide hypothesis formation and data generation.

Partners involved:
Certara UK Limited (Certara)

Available at:
Published in:
https://www.sciencedirect.com/science/article/abs/pii/S0041008X09001501?via%3Dihub

Contact:
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Logic-based dynamic modeling framework to model drug induced liver injury

Description:

Drug-induced liver injury (DILI) is the most prevalent adversity encountered in drug development and clinical settings leading to urgent needs to understand the underlying mechanisms.

We developed a modeling framework based on logic-based ordinary differential equations to study preclinical study data of DILI. The model describes the connectivity and causal activation of proteins in stress-response pathways, such as in unfolded protein response, oxidative stress, DNA damage and NF-κB pathway. Optimization is used to fit the model's prediction to the measured time-course data upon different perturbations with DILI compounds. Then, the calibrated model can be used to understand the differences between the molecular mechanism of action of the different drugs, simulate the effect of knockouts and to design new experiments based on the collected information.

To ease the use of the modeling for non-modeling experts, we also implemented a graphical user interface in R-shiny which allows to build models of cellular signaling using CellNopt.

Partners involved:
Universitaetsklinikum Heidelberg (UKHD), University of Leiden (UL)

Available at BioModels platform:
https://www.ebi.ac.uk/biomodels/MODEL2206070001

and GitHub
https://github.com/saezlab/LogicODE_GFP_SR

Contact:
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Lukas Surya Wijaya: l.s.wijaya@lacdr.leidenuniv.nl
Panuwat Trairatphisan: panuwat.trairatphisan@gmail.com

For further details, see:
https://www.sciencedirect.com/science/article/pii/S0006295221001970?via%3Dihub

Physiologically-based pharmacokinetic (PBPK) models

Human/Mouse/Rat APAP PBPK models

Description:

Acetaminophen (APAP), also known as paracetamol, is well known for its association with hepatotoxicity. We developed a Simcyp model for APAP dosing in human, mouse and rat that also incorporated reactive metabolites, specifically NAPQI, APAP-sulphate, and APAP-glucuronide. The model can be used to output total hepatic APAP and metabolite burden to obtain species specific oral equivalent doses. This Simcyp model can also facilitate creating exposure linked toxicodynamic models linked to the APAP model outputs (parent or metabolite) to explore downstream effects of exposure, such as depletion of cofactors, depletion of glutathione, and feedback with NRf2-mediated adaption.

Partners involved:
Certara UK Limited (Certara)

Available at:
Simcyp Simulator (Human, Animal):
https://www.certara.com/software/simcyp-pbpk/

Contact:
Heeseung Jo: emily.jo@certara.com
Iain Gardner: iain.gardner@certara.com
Dennis Reddyhoff: dennis.reddyhoff@certara.com

For further details, see the precursor model in BioModels:
https://www.ebi.ac.uk/biomodels/BIOMD0000000609

Kidney models
TransQST Work Package 6

Systems models

Translational Quantitative System Toxicology (QST) model for Drug-Induced Kidney Injury (DIKI)

Description:

Renal toxicity is one of the major causes of drug attrition while no translational model for DIKI had been developed to date. The TransQST WP6 (Work Package 6) team developed a prototype of kidney QST model based on the newly generated dose-response and time-course toxicity data from cisplatin in rats. The model can predict the degrees of lesions on renal proximal tubules associated to serum and urinary injury biomarkers in rats while these findings can also be translated to human applying species-specific physiological parameters. Potential applications of the kidney QST model include study design support (e.g., dose selection and prediction of recovery time) and renal injury biomarker monitoring in human patients.

Partners involved:
AbbVie Deutschland GmbH & Co. KG (Abbvie), Certara UK Limited (Certara), University of Leiden (UL)

Available at BioModels repository:
https://www.ebi.ac.uk/biomodels/MODEL2204290001

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Ciaran Fisher: ciaran.p.fisher@gsk.com
Heeseung Jo: emily.jo@certara.com

Physiologically-based pharmacokinetic (PBPK) models

PBPK model cisplatin and PBPK model carboplatin

Description:

Both cisplatin and carboplatin are platinum-based cancer drugs, yet cisplatin dosing presents more severe nephrotoxicity than from carboplatin dosing. Physiologically based pharmacokinetic (PBPK) modelling was used to explore potential exposure driven mechanisms for this discrepancy. This PBPK modelling framework describes known mechanism of parent compound hydrolysing to hydrated complexes (grouped “mobile metabolites”) and irreversible binding to proteins (grouped “fixed metabolites”). This model also incorporated higher cisplatin induced kidney exposure of platinum due to transporter action which is not relevant for carboplatin. This framework allowed recovery of platinum concentrations after cisplatin and carboplatin dosing in systemic circulation and kidneys in both human and rat. Indeed, this model identified significantly higher platinum exposure in the kidneys from cisplatin than from carboplatin.

Partners involved:
Certara UK Limited (Certara)

Available at:
Plan to be published as part of kidney QST model manuscript (Translational Quantitative System Toxicology (QST) model for Drug-Induced Kidney Injury (DIKI)). Currently model in QSP (Quantitative Systems Pharmacology) format at Certara

Contact:
Heeseung Jo: emily.jo@certara.com

For further details, see:
https://www.sciencedirect.com/science/article/abs/pii/0378427488900240?via%3Dihub

Human PBPK model cyclosporine A

Description:

Cyclosporine A (CsA) is an immunosuppressive medication used to prevent rejection in organ transplants. However, therapeutic monitoring is required to prevent drug-induced nephrotoxicity. A PBPK model for CsA dosing in human is available through the Simcyp Simulator and validated against known concentration time profiles from intravenous and oral dosing. CsA elimination is primarily driven through CYP3A4 facilitated metabolism and includes CsA inhibitory potential against various metabolizing enzymes and transporters. This model also includes PBPK models for two metabolites from CsA: M1 and M17, with inhibition data against transporters incorporated for M1.

Partners involved:
Certara UK Limited (Certara)

Available at:
Model available in Simcyp Simulator V19, at Certara

Contact:
Heeseung Jo: emily.jo@certara.com
Iain Gardner: iain.gardner@certara.com

For further details, see:
Earlier v. (V14) of compound use published:
https://pubmed.ncbi.nlm.nih.gov/32055591/

Rat PBPK model cyclosporine A

Description:

In *vitro* cyclosporine A (CsA) has been shown to cause toxicity and oxidative stress in Renal Proximal Tubule Epithelial Cells (RPTECs) but transcriptome changes consistent with oxidative stress were not observed in the rat in vivo. We used physiologically based pharmacokinetic (PBPK) models to investigate whether the pharmacokinetics of CsA could explain this discrepancy. This model incorporated known non-linearity in clearance as well as in blood and tissue binding. A full body PBPK model incorporating this non-linearity in binding and a perfusion limited PBPK model was developed. The non-linear binding model was developed in Simulink (Matlab, MathWorks) by integrating the Simcyp Simulator's full PBPK model for rat with nonlinear intracellular drug binding. For both models the predicted concentrations in kidney tissue in vivo is lower than the concentrations causing toxicity and oxidative stress in vitro, which may explain the discrepancy in toxicity presentation.

Partners involved:
Certara UK Limited (Certara)

Available at:
Model currently not available

Contact:
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For further details, see:
https://www.certara.com/app/uploads/2019/09/Ferreira_2018_Consortium_cyclosporine.pdf

Heart models
TransQST Work Package 7

Systems models

Hemodynamic cardiovascular systems modeling framework

Description:

Cardiovascular safety studies in preclinical animal models are of crucial importance to determine non-QT cardiovascular hemodynamic effects of investigational drugs. We developed a mathematical modelling framework to support identification of the cardiovascular mode-of-action from preclinical study data, and to support cross-species translation between preclinical species and humans. The model can also be used to design efficient preclinical studies. To enhance use of the model by non-modelling cardiovascular safety experts, we implemented the model as web-application to support design of novel cardiovascular safety studies and subsequent interpretation of data obtained.

Partners involved:
University of Leiden (UL)

Available at BioModels repository:
https://github.com/vanhasseltlab/hemodynamic-simulator
The Web application can be accessed through:
https://hemosim.lacdr.leidenuniv.nl/

Contact:
Coen van Hasselt: coen.vanhasselt@lacdr.leidenuniv.nl

For further information see:
https://pubmed.ncbi.nlm.nih.gov/35213797/

Systems models included in the Virtual Assay Tool

Purkinje Fiber Model

Description:

This model reproduces human cardiac Purkinje electrophysiology, incorporates detailed Purkinje-specific ionic currents and Calcium handling, and was validated using experimental data from human cardiac Purkinje fibres. It can be used for in silico prediction and/or mechanistic investigation into drug-induced electrophysiological changes and proarrhythmic risk stratification for multichannel ion channel blockers/modulators in healthy or diseased conditions (HF, MI, HCM).

Partners involved:
The Chancellor, Master and Scholars of the University of Oxford (UOXF)

Available at:
Available as part of Virtual Assay (free for academics) and CellML. Matlab available upon request.

Contact:
Blanca Rodriguez: blanca.rodriguez@cs.ox.ac.uk

For further details, see:
https://www.jmcc-online.com/article/S0022-2828(20)30083-3/fulltext

ToR-Ord Model

Description:

This model reproduces human cardiac ventricular electrophysiology and was developed to improve the response to sodium channel blocks and agreement with AP biomarkers from human experimental data, compared to previous models (O'Hara et al., 2011). It can be used for in silico prediction and/or mechanistic investigation into drug-induced electrophysiological changes and proarrhythmic risk stratification for multichannel ion channel blockers/modulators in healthy or diseased conditions (HF, MI, HCM).

Partners involved:
The Chancellor, Master and Scholars of the University of Oxford (UOXF)

Available at:
Available as part of Virtual Assay (free for academics), CellML, and GitHub:
https://github.com/jtmff/torord

Contact:
Blanca Rodriguez: blanca.rodriguez@cs.ox.ac.uk

For further details, see:
https://elifesciences.org/articles/48890

Enhanced ToR-ORd model with contractility included

Description:

This model allows for predictions of drug-induced positive/negative inotropic effects, based on ion channel information, and was validated using pre-clinical and clinical data. It can be used for in silico prediction and/or mechanistic investigation into drug-induced electrophysiological and contractility changes (for efficacy prediction) and proarrhythmic risk stratification for multichannel ion channel and/or contractility blockers/modulators in healthy or diseased conditions (HF, MI, HCM).

Partners involved:
The Chancellor, Master and Scholars of the University of Oxford (UOXF)

Available at:
Available as part of Virtual Assay (free for academics) and Matlab (available upon request).

Contact:
Blanca Rodriguez: blanca.rodriguez@cs.ox.ac.uk

For further details, see:
https://www.sciencedirect.com/science/article/pii/S007961072030064X?via%3Dihub

Physiologically-based pharmacokinetic (PBPK) model

Cardiac PBPK permeability-limited model

Description:

Physiologically based pharmacokinetic (PBPK) models can be used to predict local tissue concentrations, specifically the concentration within the target tissues of toxic endpoints. Cardioactive drugs may elicit their effects by binding to receptors, ion channels, enzymes, or other targets from either the extracellular or intracellular side of the sarcolemma. Because the sarcolemma may act as a permeability barrier and active transport may be involved in a drug's distribution within cardiac tissue, a multi-compartment cardiac permeability-limited model was developed to address these issues. Being developed as an academic exercise it was enhanced and implemented in the Simcyp Simulator software (Certara UK) as a part of the TransQST project to support the cardiac safety assessment of new compounds at the preclinical stage of drug development.

Partners involved:
Certara UK Limited (Certara)

Available at:
The application is freely available at
https://github.com/jszlek/CardiacPBPK

https://sourceforge.net/projects/cardiacpbpk/
This open-source application runs on all platforms supporting R-environment (Linux, Windows, Mac OS X, Solaris).

Contact:
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For further details, see:
https://www.nature.com/articles/srep39494

https://www.sciencedirect.com/science/article/abs/pii/S0010482519303531?via%3Dihub

Gastro-intestinal immune system models TransQST Work Package 8

Agent-based Model

Multi-scale GI epithelial model

Description:

A multi-scale agent-based model (ABM) of the gastro-intestinal epithelium with the capability to simulate the disruption of molecular events in individual cells and its propagation across multiple levels of epithelial organization. The model incorporates multiple clinically relevant signalling pathways, such as Wnt, Notch, BMP, RNF43/ZNRF3 and contact inhibition, the intracellular cell cycle protein network and DNA and RNA kinetics in each single cell. Single cells respond to molecular cues to proliferate and differentiate while interacting in the 3-D geometry of the crypt and migrating towards the villus. The signalling pathways and/or cell cycle protein network and/or DNA/RNA synthesis can be mechanistically perturbed to simulate disease or the response to drug challenges, with the severity and duration of the resulting epithelial damage used for the prediction of GI adverse outcomes such as clinical diarrhoea. The model can be used for research into drug mechanisms of action or diseases, or in the drug discovery process for early (pre-)clinical translation and dosing strategies.

Partners involved:
AstraZeneca AB (AZ)

Contact:
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Available at BioModels repository:
https://www.ebi.ac.uk/biomodels/MODEL2212120002

Ordinary Differential Equation (ODE) models

Modified Shankaran 2017 model

Description:

Evaluation and further development of the Shankaran et al. 2017 model. Gastrointestinal toxicities can be dose limiting for some compounds and this can necessitate careful design of dosing regimens to maximise efficacy while maintaining tolerability. The Shankaran et al. 2017 intestinal epithelial cell turnover model was published at the start of the transQST project with its ability to apply translational modelling to predict clinical incidence of diarrhoea from pre-clinical rodent data demonstrated for irinotecan. This model was further explored and extended throughout the transQST project, both to fully understand its predictive abilities and to act as a benchmark (in being a model which was available at the start of the project) to allow the added value of the new models created within the transQST project to be compared against. The key areas of focus for this model have been on evaluating its ability to predict the response to compounds other than irinotecan (for which it was originally published), exploring the predictive ability of the model when using alternative model input data (in particular data derived from organoids), and the model was also extended to add citrulline as a model output.

Partners involved:
GSK PLC (GSK), AstraZeneca AB (AZ), Certara UK Limited (Certara), Janssen Pharmaceutica NV (Janssen), University of Liverpool (ULIV), University of Maastricht (UM), Boehringer Ingelheim GmbH (BI)

Available at:
Original Shankaran model and code published in:
https://ascpt.onlinelibrary.wiley.com/doi/10.1002/psp4.12255

https://ascpt.onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fpsp4.12255&file=psp412255-sup-0002-suppinfo02.txt
Code for modified model will be included as part of any future publication of this work.

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Multi-scale epithelial GI model

Description:

A compartmental modelling framework that describes the dynamics of cell proliferation, differentiation and migration into the villus and integrates heterogeneous epithelial-related processes, such as epithelial transcriptional profile, citrulline kinetics, epithelial permeability, and probability of diarrhoea. The model describes the disturbance of these processes responding to drug challenges affecting epithelial dynamics and enables the translation of pre-clinical drug-induced epithelial toxicity into clinical safety at early stages of the drug development pipeline.

Partners involved:
AstraZeneca AB (AZ)

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Available at BioModels repository:
https://www.ebi.ac.uk/biomodels/MODEL2212120003

Drug-induced gastrointestinal acute inflammation modeling framework

Description:

Epithelial damage and inflammatory response are key characteristics of drug-induced gastrointestinal injury. We here report a mathematical modelling framework that describes the dynamic behavior of the GI epithelial cell lineage and concurrent acute inflammation represented by polymorphonuclear leukocytes (PMNs) after the drug exposure. The model can serve as a useful tool to quantitatively evaluate the drug toxicity in the GI tract and thus to support various decisions during drug development, such as toxicology study design and safe dose selection.

Partners involved:
Boehringer Ingelheim GmbH (BI) - primary developer and data provider. Janssen Pharmaceutica NV (Janssen) - data provider.

Available at:
Current version of the model is being finalized and stored in the internal model repository in the Nonclinical Drug Safety-US department of BI. Also available on the project SharePoint for consortium internal use.

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TransQST Tools

The development and enhancement of tools that help to decipher and quantify toxic mechanisms is another key achievement of the project. Most of these tools have already been published and are openly accessible. To facilitate the access, the consortium has made them available through the open-source platform bio.tools, allowing their use in other projects and by the wider scientific community[9].

The consortium has successfully developed and enhanced a wide range of tools that help to decipher and quantify toxic mechanisms.

9 https://bio.tools/t?page=1&q=%27TransQST%27&sort=score

TransQST developed tools

TXG-MAPr

Description:

Toxicogenomic data in safety testing represent a critical source to uncover underlying mechanisms of drug-induced toxicities. Association of gene co-expression networks that are predictive of liver/kidney pathology later is expected to impact lead optimization and enable prioritization of drug candidates which are less likely to induce pathology. In this sense, TransQST has been successful in developing Weighted Correlation Network Analysis (WGCNA) based TXG-MAPr tools, which contribute to improved drug discovery and development pipelines, leading to safer and faster medicines. TXG-MAPr currently comprises three different tools to study Primary Human Hepatocytes, DILI (drug-induced liver injury) and DIKI (drug-induced kidney injury). In the TXG-MAPr tools, users can analyse dose- and time-response curves, compound correlation plots and functional annotation of the WGCNA modules to derive mechanistic information of the toxicity. In addition, the tools also include the prediction of transcription factor activities, as well as physical interactions between downstream proteins encoded by the transcriptome, which might be useful in analysing the perturbations triggered by exposure with toxic compounds. Users can upload external/in-house expression data to investigate module perturbation by looking at the module eigengene scores (EGS) and compare it to the TG-GATEs compounds to investigate similarities in mode of action. The tools have been co-developed between TransQST, eTRANSAFE and EU-ToxRisk projects.

Partners involved:
University of Leiden (UL), AbbVie Deutschland GmbH & Co. KG (Abbvie), Eli Lilly and Company Ltd (Eli-Lilly)

Available to consortium partners at:
https://txg-mapr.eu/

https://bio.tools/TXG-MAPr

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For further details, see:
https://link.springer.com/article/10.1007/s00204-021-03141-w

iPath

Description:

The iPath modelling approach aims to identify cellular pathways involved in drug toxicity, providing mechanistic hypotheses for drug adverse events. iPath identifies pathways in functional networks that connect drug targets, off-targets, ADME proteins and proteins associated with the toxicity phenotype elicited by a drug. It leverages information from diverse omics datasets, namely protein interaction networks, toxicogenomic data, gene and protein expression data, genotype-phenotype associations, and chemical biology information. iPath as input tissue/organ-specific protein interaction networks and a list of genes of interest, and after mapping the seeds to the network it applies network optimisation algorithms to identify the subnetwork.

Partners involved:
Hospital del Mar Medical Research Institute (IMIM)

Available at:
https://bio.tools/ipath_IMIM

http://sbi.imim.es/data/ipath.tgz

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Path4Drug

Description:

Path4Drug is a workflow involving a computational technique that employs propagation of drug-protein and protein-protein interactions to predict the biological pathways that are affected by a drug or compound. Reliable, openly available repositories (CHEMBL, TTD, DrugBank, PharmGKB, IUPHAR, Intact, MINT) were used for connecting pharmaceutically relevant compounds to their target proteins in human and the target proteins to their first-degree interactors. Since these databases differ in their architecture and accessibility, diverse sub-workflows with filtering steps were created ensuring the quality of the retrieved data.

Partners involved:
University of Vienna (UNIVIE), European Bioinformatics Institute, European Molecular Biology Laboratory (EMBL-EBI)

Available at:
https://bio.tools/Path4Drug

https://kni.me/s/7jbMNHvalhE2ZCtU

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For further details, see:
https://www.frontiersin.org/articles/10.3389/fphar.2021.708296/full

BioModels Parameters

Description:

One of the major bottlenecks in building systems biology models is identification and estimation of parameters for model calibration, an essential, yet laborious task. BioModels Parameters is a resource that facilitates easy search and retrieval of parameter values used in the SBML (Systems Biology Markup Language) models stored in the BioModels repository. Users can search for a model entity (e.g., a protein or drug) to retrieve the rate equations describing it, as well as the associated parameter values and the initial concentration from the SBML models in BioModels. The BioModels Parameters table provides a quick overview of available parameter values for guidance – the original model should be referred to understand the complete context of the parameter usage.

Partners involved:
European Bioinformatics Institute, European Molecular Biology Laboratory (EMBL-EBI)

Available at:
https://bio.tools/biomodels-parameter

https://www.ebi.ac.uk/biomodels/parameterSearch

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For further details, see:
https://dx.doi.org/10.1093/BIOINFORMATICS/BTAA560

Carnival

Description:

CARNIVAL (CAusal Reasoning for Network identification using Integer VALue programming) is a method for the identification of upstream regulatory signalling pathways from downstream gene expression (GEX). The aim of the CARNIVAL pipeline is to identify a subset of interactions from a prior knowledge network that represent potential regulated pathways linking known or potential targets of perturbation towards active transcription factors derived from GEX data. Applications of CARNIVAL include the identification of drug's modes of action and of deregulated processes in diseases (even if the molecular targets remain unknown) by deciphering the alterations of main signalling pathways as well as alternative pathways and off-target effects.

Partners involved:
University of Heidelberg (UKHD)

Available at:
https://bio.tools/CARNIVAL

https://github.com/saezlab/CARNIVAL

https://bioconductor.org/packages/release/bioc/html/CARNIVAL.html

Contact:
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For further details, see:
https://www.nature.com/articles/s41540-019-0118-z

Tools enhanced by the TransQST consortium

OmniPath

Description:

The information about the roles of proteins in diseases, their expression in different tissue types, intracellular localizations, interaction partners etc. is scattered across many different databases. These databases all provide the data in different formats and under various licensing schemes. Omnipath reduces the complexity to access this information by integrating more than a hundred of these databases, providing a single access point to all of them through web-interface, from R, python and Cytoscape with clear licensing information for academia and industry. The focus of Omnipath is on literature curated human and rodent signalling pathways and it provides access to knowledge spanning intra- and intercellular processes for data analysis. Omnipath has also been used as a basis to create other TransQST modeling tools such as CARNIVAL and COSMOS (Causal Oriented Search of Multi Omic Space).

Partners involved:
University of Heidelberg (UKHD)

Available at:
https://bio.tools/OmniPath

https://omnipathdb.org/

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omnipathdb@gmail.com

For further details, see:
https://www.embopress.org/doi/full/10.15252/msb.20209923

Cosmos

Description:

The multi-omics characterization of drug induced molecular effects became more abundant in recent years. Although many tools are available to analyse the effect of the drug on a single omics layer, trans-omic analysis, i.e., analysing the regulation of processes across multiple omics layers, is still not straightforward. To tackle this issue, COSMOS (Causal Oriented Search of Multi-Omic Space) aims to integrate multi-omics datasets. The tool uses optimization to find a context specific network that is coherent with prior knowledge information about possible interactions and with measurement data. It is a method that integrates phosphoproteomics, transcriptomics, and metabolomics data sets and leverages extensive prior knowledge of signalling pathways, metabolic networks, and gene regulation with computational methods to estimate activities of transcription factors and kinases as well as network-level causal reasoning. The COSMOS pipeline can provide mechanistic explanations for experimental observations across multiple omics data sets.

Partners involved:
University of Heidelberg (UKHD)

Available at:
https://bio.tools/cosmos-omics

https://saezlab.github.io/cosmosR

https://bioconductor.org/packages/release/bioc/html/cosmosR.html

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For further details, see:
https://www.embopress.org/doi/full/10.15252/msb.20209730

CellNOptR

Description:

Modelling time course perturbation data of cell signalling is challenging due to the large computational complexity and uncertainty in the mechanisms of signalling. CellNOptR is an open-source R software package for building predictive logic models of signalling networks by training networks derived from prior knowledge to signalling data. CellNOptR features different logic formalisms, from Boolean models to differential equations, in a common framework. These different logic model representations accommodate state and time values with increasing levels of detail. Models built with CellNOptR are useful tools to understand how signals are processed by cells and how this is altered in disease. They can be used to predict the effect of perturbations (individual or in combinations), and potentially to engineer therapies that have differential effects/side effects depending on the cell type or context.

Partners involved:
University of Heidelberg (UKHD)

Available at:
https://bio.tools/cellnoptr

http://bioconductor.org/packages/release/bioc/html/CellNOptR.html

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julio.saez@uni-heidelberg.de

For further details, see:

https://bmcsystbiol.biomedcentral.com/articles/10.1186/1752-0509-6-133

BioModels database

Description:

Database of annotated published models. BioModels is a data resource that allows biologists to store, search and retrieve published mathematical models of biological interests. Models present in this database are annotated and linked to relevant data resources, such as publications, databases of compounds and controlled vocabularies; modelling formats can be converted, with some of them being available online to be used directly. BioModels is the selected repository for the sustainability of TransQST-developed models. The aim is to make as many project models available as possible once they have been published.

Partners involved:
European Bioinformatics Institute, European Molecular Biology Laboratory (EMBL-EBI)

Available at:
https://bio.tools/biomodels

https://www.ebi.ac.uk/biomodels/

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For further details, see:
https://academic.oup.com/nar/article/48/D1/D407/5614569

https://bmcsystbiol.biomedcentral.com/articles/10.1186/1752-0509-4-92

https://academic.oup.com/nar/article/46/D1/D1248/4584626

Virtual Assay

Description:

The Virtual Assay provides predictions of drug safety and efficacy based on ion channel information. The software provides a framework to run in silico drug trials in populations of human cardiac cell models. Virtual Assay starts with well-understood human cellular biology models and modulates the variables to generate a range, or population, of models, which will respond differently to the same inputs.

These populations are then calibrated against experimental data, retaining only those models in Calibrated Model Populations range with experimental observations. Once calibrated, these populations can be used to analyse the effects of different pharmaceutical agents on cellular response at the population level.

Partners involved:
University of Oxford (UOXF)

Available at:
https://bio.tools/virtual_assay

https://www.cs.ox.ac.uk/ccs/virtual-assay/

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For further details, see:
https://www.sciencedirect.com/science/article/pii/S1877750320305032?via%3Dihub

DisGeNET

Description:

Prioritizing information on targets associated with diseases and identification of their toxicity profiles are major bottlenecks in drug R&D. DisGeNET, as a knowledge platform that aggregates and standardizes data about disease-associated genes and variants from multiple authoritative sources, complemented with the most recent findings extracted from the scientific literature by text mining, facilitates these processes and therefore expedites decision making in drug R&D. DisGeNET is a discovery platform containing one of the largest publicly available collections of genes and variants associated with human diseases. DisGeNET integrates data from expert curated repositories, GWAS (Genome Wide Association Study) catalogues, animal models and the scientific literature. DisGeNET data are homogeneously annotated with controlled vocabularies and community-driven ontologies. Additionally, several original metrics are provided to assist the prioritization of genotype–phenotype relationships. The current version of DisGeNET (v7.0) contains 1,134,942 gene-disease associations (GDAs), between 21,671 genes and 30,170 diseases, disorders, traits, and clinical or abnormal human phenotypes, and 369,554 variant-disease associations (VDAs), between 194,515 variants and 14,155 diseases, traits, and phenotypes. The spin-off company Medbioinformatics Solutions SL was built on the success of DisGENET, and provides a new commercial version of the platform, DISGENET plus (https://www.disgenetplus.com/).

Partners involved:
Hospital del Mar Medical Research Institute (IMIM)

Available at:
https://bio.tools/disgenet

https://www.disgenet.org/

https://www.disgenetplus.com

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For further details, see:
https://academic.oup.com/database/article/doi/10.1093/database/bav028/2433160

https://academic.oup.com/nar/article/48/D1/D845/5611674

https://www.sciencedirect.com/science/article/pii/S2001037021001963?via%3Dihub

Data curated and generated in TransQST

The overarching aim for TransQST defined at the start of the initiative was to gather existing data and generate new data under the project goals to support the development of tools and models to facilitate safety assessment of drug candidates before they enter the clinical testing phase.

A large number of datasets of different types have been both curated and generated during the project and made accessible as much as possible through public resources, allowing their wider use beyond TransQST.

Omics data:

Gene expression data for liver, kidney, heart, and gastrointestinal tract that have been generated by, or curated within, the TransQST consortium are available via ArrayExpress[10].

High-quality datasets with further curation and visualization are linked to the Expression Atlas Knowledge Base from the rightmost column ("Atlas") in the query results above.

Proteomics data that have been generated by the TransQST consortium is available via PRIDE[11].

Drug warning data:

Data for withdrawn drugs or drugs with black box warnings that have been curated by the TransQST consortium is available via ChEMBL[12].

Additional data:

Additional data for liver, kidney, heart, and gastrointestinal tract that have been generated by, or curated within, the TransQST consortium includes histopathology, clinical chemistry, toxicokinetics, hemodynamic, and ion channel information. It is available via BioStudies[13].

10 https://www.ebi.ac.uk/biostudies/arrayexpress/studies

11 https://www.ebi.ac.uk/pride/archive?keyword=TransQST

12 https://www.ebi.ac.uk/chembl/web_components/explore/drug_warnings

13 https://www.ebi.ac.uk/biostudies/studies/?facet.collection=transqst

List of publications

Seventy peer-reviewed research articles based on project results have been published by TransQST members by the time of releasing the present booklet in January 2023.

For an updated list of publications after project end, please consult TransQST publications list on Europe PMC[14].

1. Maldonado EM, Leoncikas V, Fisher CP, Moore JB, Plant NJ, Kierzek AM. Integration of genome scale metabolic networks and gene regulation of metabolic enzymes with physiologically based pharmacokinetics. CPT Pharmacometrics Syst Pharmacol. 2017; 6(11):732-746.

2. Passini E, Britton OJ, Lu HR, Rohrbacher J, Hermans AN, Gallacher DJ, Greig RJH, Bueno-Orovio A, Rodriguez B. Human in silico drug trials demonstrate higher accuracy than animal models in predicting clinical pro-arrhythmic cardiotoxicity. Front Physiol. 2017; 8:668.

3. Aguirre-Plans J, Piñero J, Menche J, Sanz F, Furlong LI, Schmidt HHHW, Oliva B, Guney E. Proximal pathway enrichment analysis for targeting comorbid diseases via network endopharmacology. Pharmaceuticals (Basel). 2018; 11(3): E61.

4. Yin A, Yamada A, Stam WB, van Hasselt JGC, van der Graaf PH. Quantitative systems pharmacology analysis of drug combination and scaling to humans: the interaction between noradrenaline and vasopressin in vasoconstriction. Br J Pharmacol. 2018; 175(16):3394-3406.

5. Piñero J, Furlong LI, Sanz F. In silico models in drug development: where we are. Curr Opin Pharmacol. 2018; 42:111-121.

6. Piñero J, Gonzalez-Perez A, Guney E, Aguirre-Plans J, Sanz F, Oliva B, Furlong LI. Network, transcriptomic and genomic features differentiate genes relevant for drug response. Front Genet. 2018; 9:412.

7. Pastor M, Quintana J, Sanz F. Development of an infrastructure for the prediction of biological endpoints in industrial environments. Lessons learned at the eTOX project. Front Pharmacol. 2018; 9:1147.

8. Copple IM, den Hollander W, Callegaro G, Mutter FE, Maggs JL, Schofield AL, Rainbow L, Fang Y, Sutherland JJ, Ellis EC, Ingelman-Sundberg M, Fenwick SW, Goldring CE, van de Water B, Stevens JL, Park BK. Characterisation of the NRF2 transcriptional network and its response to chemical insult in primary human hepatocytes: implications for prediction of drug-induced liver injury. Arch Toxicol. 2018; 93(2):385-399.

9. Souza T, Trairatphisan P, Piñero J, Furlong LI, Saez-Rodriguez J, Kleinjans J, Jennen D. Embracing the dark side: computational approaches to unveil the functionality of genes lacking biological annotation in drug-induced liver injury. Front Genet. 2018; 9:527.

10. Zhou X, Qu Y, Passini E, Bueno-Orovio A, Liu Y, Vargas HM, Rodriguez B. Blinded in silico drug trial reveals the minimum set of ion channels for torsades de pointes risk assessment. Front Pharmacol. 2019; 10:1643.

11. IMEx Consortium Curators, Del-Toro N, Duesbury M, Koch M, Koch M, Perfetto L, Shrivastava A, Ochoa D, Wagih O, Piñero J, Kotlyar M, Pastrello C, Beltrao P, Furlong LI, Jurisica I, Hermjakob H, Hermjakob

14 https://europepmc.org/search?query=%28GRANT_ID%3A%22116030%E2%80%9D%20OR%20%22H2020-IMI-2%20116030%22%29%20OR%20%28%22TransQST%22%29%20OR%20%28%22grant%20 agreement%20no.%20116030%22%29%20OR%20%28%22grant%20agreement%20116030%22%29%20OR%20%28%22grant%20No.%20116030%22%29%20OR%20%28%22grants%20agreements%20 no.%20116030%22%29%20OR%20%28DOI%3A%2210.14573%2Faltex.2107261%22%20OR%20%2210.1016%2Fj.jmb.2020.09.015%22%20OR%20%2210.1016%2Fj.coph.2018.08.007%22%29

H, Orchard S, Porras P. Capturing variation impact on molecular interactions in the IMEx Consortium mutations data set. Nat Commun. 2019; 10(1):10.

12. Aguirre-Plans J, Piñero J, Sanz F, Furlong LI, Fernandez-Fuentes N, Oliva B, Guney E. GUILDify v2.0: a tool to identify molecular networks underlying human diseases, their comorbidities and their druggable targets. J Mol Biol. 2019; 431(13):2477-2484.

13. Rodrigues D, Souza T, Jennen DGJ, Lemmens L, Kleinjans JCS, de Kok TM. Drug-induced gene expression profile changes in relation to intestinal toxicity: State-of-the-art and new approaches. Cancer Treat Rev. 2019; 77:57-66.

14. Albrecht W, Kappenberg F, Brecklinghaus T, Stoeber R, Marchan R, Zhang M, Ebbert K, Kirschner H, Grinberg M, Leist M, Moritz W, Cadenas C, Ghallab A, Reinders J, Vartak N, van Thriel C, Golka K, Tolosa L, Castell JV, Damm G, Seehofer D, Lampen A, Braeuning A, Buhrke T, Behr AC, Oberemm A, Gu X, Kittana N, van de Water B, Kreiling R, Fayyaz S, van Aerts L, Smedsrød B, Ellinger-Ziegelbauer H, Steger-Hartmann T, Gundert-Remy U, Zeigerer A, Ullrich A, Runge D, Lee SML, Schiergens TS, Kuepfer L, Aguayo-Orozco A, Sachinidis A, Edlund K, Gardner I, Rahnenführer J, Hengstler JG. Prediction of human drug-induced liver injury (DILI) in relation to oral doses and blood concentrations. Arch Toxicol. 2019; 93(6):1609-1637.

15. Passini E, Trovato C, Morissette P, Sannajust F, Bueno-Orovio A, Rodriguez B. Drug-induced shortening of the electromechanical window is an effective biomarker for in silico prediction of clinical risk of arrhythmias. Br J Pharmacol. 2019; 176(19):3819-3833.

16. Liu A, Trairatphisan P, Gjerga E, Didangelos A, Barratt J, Saez-Rodriguez J. From expression footprints to causal pathways: contextualizing large signaling networks with CARNIVAL. NPJ Syst Biol Appl. 2019; 5:40.

17. Leishman DJ. Improving prediction of torsadogenic risk in the CiPA in silico model by appropriately accounting for clinical exposure. J Pharmacol Toxicol Methods. 2019; 101:106654.

18. Tomek J, Bueno-Orovio A, Passini E, Zhou X, Minchole A, Britton O, Bartolucci C, Severi S, Shrier A, Virag L, Varro A, Rodriguez B. Development, calibration, and validation of a novel human ventricular myocyte model in health, disease, and drug block. Elife. 2019; 8:e48890.

19. Malik-Sheriff RS, Glont M, Nguyen TVN, Tiwari K, Roberts MG, Xavier A, Vu MT, Men J, Maire M, Kananathan S, Fairbanks EL, Meyer JP, Arankalle C, Varusai TM, Knight-Schrijver V, Li L, Dueñas-Roca C, Dass G, Keating SM, Park YM, Buso N, Rodriguez N, Hucka M, Hermjakob H. BioModels-15 years of sharing computational models in life science. Nucleic Acids Res. 2020; 48(d1):D407-D415.

20. Lucendo-Villarin B, Nell P, Hellwig B, Filis P, Feuerborn D, O'Shaughnessy PJ, Godoy P, Rahnenführer J, Hengstler JG, Cherianidou A, Sachinidis A, Fowler PA, Hay DC. Genome-wide expression changes induced by bisphenol A, F and S in human stem cell derived hepatocyte-like cells. EXCLI J. 2020; 19: 1459–1476.

21. Piñero J, Ramírez-Anguita JM, Saüch-Pitarch J, Ronzano F, Centeno E, Sanz F, Furlong LI. The DisGeNET knowledge platform for disease genomics: 2019 update. Nucleic Acids Res. 2020; 48(d1):D845-D855.

22. Ferreira S, Fisher C, Furlong LI, Laplanche L, Park BK, Pin C, Saez-Rodriguez J, Trairatphisan P. Quantitative systems toxicology modeling to address key safety questions in drug development: A focus of the TransQST Consortium. Chem Res Toxicol. 2020; 33(1):7-9.

23. Buhl EM, Djudjaj S, Klinkhammer BM, Ermert K, Puelles VG, Lindenmeyer MT, Cohen CD, He C, Borkham-Kamphorst E, Weiskirchen R, Denecke B, Trairatphisan P, Saez-Rodriguez J, Huber TB, Olson LE, Floege J, Boor P. Dysregulated mesenchymal PDGFR-β drives kidney fibrosis. EMBO Mol Med. 2020; 12(3):e11021.
24. Trovato C, Passini E, Nagy N, Varró A, Abi-Gerges N, Severi S, Rodriguez B. Human purkinje in silico model enables mechanistic investigations into automaticity and pro-arrhythmic abnormalities. J Mol Cell Cardiol. 2020; 142:24-38.

25. Paci M, Passini E, Klimas A, Severi S, Hyttinen J, Rodriguez B, Entcheva E. All-Optical electrophysiology refines populations of in silico human iPSC-CMs for drug evaluation. Biophys J. 2020; 118(10):2596-2611.

26. Cirillo D, Catuara-Solarz S, Morey C, Guney E, Subirats L, Mellino S, Gigante A, Valencia A, Rementeria MJ, Chadha AS, Mavridis N. Sex and gender differences and biases in artificial intelligence for biomedicine and healthcare. NPJ Digit Med. 2020; 3:81.
27. Margara F, Wang ZJ, Levrero-Florencio F, Santiago A, Vázquez M, Bueno-Orovio A, Rodriguez B. In-silico human electro-mechanical ventricular modelling and simulation for drug-induced pro-arrhythmia and inotropic risk assessment. Prog Biophys Mol Biol. 2020; 159:58-74.

28. Gjerga E, Trairatphisan P, Gabor A, Koch H, Chevalier C, Ceccarelli F, Dugourd A, Mitsos A, Saez-Rodriguez J. Converting networks to predictive logic models from perturbation signalling data with CellNOpt. Bioinformatics. 2020; 36(16):4523-4524.

29. Türei D, Valdeolivas A, Gul L, Palacio-Escat N, Ivanova O, Gábor A, Módos D, Korcsmáros T, Saez-Rodriguez J. Integrated intra- and intercellular signaling knowledge for multicellular omics análisis. Mol Syst Biol. 2020; 17(3):e9923.

30. Mirela-Bota P, Aguirre-Plans J, Meseguer A, Galletti C, Segura J, Planas-Iglesias J, Garcia-Garcia J, Guney E, Oliva B, Fernandez-Fuentes N. Galaxy InteractoMIX: An integrated computational platform for the study of protein-protein interaction data. J Mol Biol. 2020; 433(11):166656.

31. Glont M, Arankalle C, Tiwari K, Nguyen TVN, Hermjakob H, Malik-Sheriff RS. BioModels Parameters: a treasure trove of parameter values from published systems biology models. Bioinformatics. 2020; 36(17):4649-4654.

32. Lucendo-Villarin B, Nell P, Hellwig B, Filis P, Feuerborn D, O'Shaughnessy PJ, Godoy P, Rahnenführer J, Hengstler JG, Cherianidou A, Sachinidis A, Fowler PA, Hay DC. Genome-wide expression changes induced by bisphenol A, F and S in human stem cell derived hepatocyte-like cells. EXCLI J. 2020; 19:1459-1476.

33. Passini E, Zhou X, Trovato C, Britton OJ, Bueno-Orovio A, Rodriguez B. The virtual assay software for human in silico drug trials to augment drug cardiac testing. J. Comput. 2021; 52.

34. Paci M, Koivumäki J, Lu H, Gallacher D, Passini E, Rodriguez B. Comparison of the simulated response of three in silico human stem cell-derived cardiomyocytes models and in vitro data under 15 drug actions. Front Pharmacol. 2021; 12.

35. Aguirre-Plans J, Piñero J, Souza T, Callegaro G, Kunnen SJ, Sanz F, Fernandez-Fuentes N, Furlong LI, Guney E, Oliva B. An ensemble learning approach for modeling the systems biology of drug-induced injury. Biol Direct. 2021; 16(1):5.

36.Hunter FMI, Bento AP, Bosc N, Gaulton A, Hersey A, Leach AR. Drug safety data curation

and modeling in chembl: boxed warnings and withdrawn drugs. Chem Res Toxicol. 2021; 34(2):385-395.

37. Tiwari K, Kananathan S, Roberts MG, Meyer JP, Sharif Shohan MU, Xavier A, Maire M, Zyoud A, Men J, Ng S, Nguyen TVN, Glont M, Hermjakob H, Malik-Sheriff RS. Reproducibility in systems biology modelling. Mol Syst Biol. 2021; 17(2):e9982.

38. Wang ZJ, Santiago A, Zhou X, Wang L, Margara F, Levrero-Florencio F, Das A, Kelly C, Dall'Armellina E, Vazquez M, Rodriguez B. Human biventricular electromechanical simulations on the progression of electrocardiographic and mechanical abnormalities in post-myocardial infarction. Europace. 2021; 23(23 suppl 1):i143-i152.

39. Hendriksen LC, Verhamme KMC, Van der Linden PD, Stricker BH, Visser LE. Women are started on a lower daily dose of metoprolol than men irrespective of dose recommendations: A potential source of confounding by contraindication in pharmacoepidemiology. Pharmacoepidemiol Drug Saf. 2021; 30(7):952-959.

40. Delaunois A, Abernathy M, Anderson WD, Beattie KA, Chaudhary KW, Coulot J, Gryshkova V, Hebeisen S, Holbrook M, Kramer J, Kuryshev Y, Leishman D, Lushbough I, Passini E, Redfern WS, Rodriguez B, Rossman EI, Trovato C, Wu C, Valentin JP. Applying the CiPA approach to evaluate cardiac proarrhythmia risk of some antimalarials used off-label in the first wave of COVID-19. Clin Transl Sci. 2021; 14(3):1133-1146.

41. Visser S, Koolen S, van Donk N, van Walree N, van der Leest C, Cornelissen R, van Schaik R, Mathijssen R, Aerts J, Stricker BH. Genetic polymorphism in ATIC is associated with effectiveness and toxicity of pemetrexed in non-small-cell lung cancer. Thorax. 2021; 76(11):1150-1153.

42. Pastor M, Gómez-Tamayo JC, Sanz F. Flame: an open source framework for model development, hosting, and usage in production environments. J Cheminform. 2021; 13(1):31.

43. de Campos-Mata L, Vaquero ST, Tachó-Piñot R, Piñero J, Grasset EK, Aldea IA, Melero NR, Carolis C, Horcajada JP, Cerutti A, Villar-García J, Magri G. SARS-CoV-2 sculpts the immune system to induce sustained virus-specific naïve-like and memory B cell responses. Clin Transl Immunology. 2021; 10(9): e1339.

44. Wijaya LS, Trairatphisan P, Gabor A, Niemeijer M, Keet J, Alcalà Morera A, Snijders KE, Wink S, Yang H, Schildknecht S, Stevens JL, Bouwman P, Kamp H, Hengstler J, Beltman J, Leist M, Le Dévédec S, Saez-Rodriguez J, van de Water B. Integration of temporal single cell cellular stress response activity with logic-ODE modeling reveals activation of ATF4-CHOP axis as a critical predictor of drug-induced liver injury. Biochem Pharmacol. 2021; 190:114591.

45. Piñero J, Saüch J, Sanz F, Furlong LI. The DisGeNET cytoscape app: Exploring and visualizing disease genomics data. Comput Struct Biotechnol J. 2021; 19:2960-2967.

46. Pin C, Collins T, Gibbs M, Kimko H. Systems modeling to quantify safety risks in early drug development: using bifurcation analysis and agent-based modeling as examples. AAPS J. 2021; 23(4):77.

47. Rodrigues D, de Souza T, Coyle L, Di Piazza M, Herpers B, Ferreira S, Zhang M, Vappiani J, Sévin DC, Gabor A, Lynch A, Chung SW, Saez-Rodriguez J, Jennen DGJ, Kleinjans JCS, de Kok TM. New insights into the mechanisms underlying 5-fluorouracil-induced intestinal toxicity based on transcriptomic and metabolomic responses in

human intestinal organoids. Arch Toxicol. 2021; 95(8):2691-2718.
48. Trairatphisan P, de Souza TM, Kleinjans J, Jennen D, Saez-Rodriguez J. Contextualization of causal regulatory networks from toxicogenomics data applied to drug-induced liver injury. Toxicol Lett. 2021; 350:40-51.

49. Musuamba FT, Skottheim Rusten I, Lesage R, Russo G, Bursi R, Emili L, Wangorsch G, Manolis E, Karlsson KE, Kulesza A, Courcelles E, Boissel JP, Rousseau CF, Voisin EM, Alessandrello R, Curado N, Dall'ara E, Rodriguez B, Pappalardo F, Geris L. Scientific and regulatory evaluation of mechanistic in silico drug and disease models in drug development: Building model credibility. CPT Pharmacometrics Syst Pharmacol. 2021; 10(8):804-825.

50. Holland CH, Ramirez Flores RO, Myllys M, Hassan R, Edlund K, Hofmann U, Marchan R, Cadenas C, Reinders J, Hoehme S, Seddek AL, Dooley S, Keitel V, Godoy P, Begher-Tibbe B, Trautwein C, Rupp C, Mueller S, Longerich T, Hengstler JG, Saez-Rodriguez J, Ghallab A. Transcriptomic cross-species analysis of chronic liver disease reveals consistent regulation between humans and mice. Hepatol Commun. 2021; 6(1):161-177.

51. Soroush N, Aarnoudse AJ, Kavousi M, Kors JA, Ikram MA, Newton-Cheh C, Ahmadizar F, Stricker BH. A NOS1AP gene variant is associated with a paradoxical increase of the QT-interval shortening effect of digoxin. Pharmacogenomics J. 2021; 22(1):55-61.

52. Callegaro G, Kunnen SJ, Trairatphisan P, Grosdidier S, Niemeijer M, den Hollander W, Guney E, Piñero Gonzalez J, Furlong L, Webster YW, Saez-Rodriguez J, Sutherland JJ, Mollon J, Stevens JL, van de Water B. The human hepatocyte TXG-MAPr: gene co-expression network modules to support mechanism-based risk assessment. Arch Toxicol. 2021; 95(12):3745-3775.

53. Füzi B, Gurinova J, Hermjakob H, Ecker GF, Sheriff R. Path4Drug: data science workflow for identification of tissue-specific biological pathways modulated by toxic drugs. Front Pharmacol. 2021; 12:708296.

54. Vrijenhoek NG, Wehr MM, Kunnen SJ, Wijaya LS, Callegaro G, Moné MJ, Escher SE, Van de Water B. Application of high-throughput transcriptomics for mechanism-based biological read-across of short-chain carboxylic acid analogues of valproic acid. ALTEX. 2022; 39(2):207–220.

55. Rodrigues D, Coyle L, Füzi B, Ferreira S, Jo H, Herpers B, Chung SW, Fisher C, Kleinjans JCS, Jennen D, de Kok TM. Unravelling Mechanisms of Doxorubicin-Induced Toxicity in 3D Human Intestinal Organoids. Int J Mol Sci. 2022; 23(3):1286.

56. Ahmadizar F, Soroush N, Ikram MA, Kors JA, Kavousi M, Stricker BH. QTc-interval prolongation and increased risk of sudden cardiac death associated with hydroxychloroquine. Eur J Prev Cardiol. 2022; 28(17):1875-1882.

57. Rodrigues D, Herpers B, Ferreira S, Jo H, Fisher C, Coyle L, Chung SW, Kleinjans JCS, Jennen DGJ, de Kok TM. A transcriptomic approach to elucidate the mechanisms of gefitinib-induced toxicity in healthy human intestinal organoids. Int J Mol Sci. 2022; 23(4):2213.

58. Fu Y, Taghvafard H, Said MM, Rossman EI, Collins TA, Billiald-Desquand S, Leishman D, van der Graaf PH, van Hasselt JGC, Snelder N. A novel cardiovascular systems model to quantify drugs effects on the inter-relationship between contractility and other hemodynamic variables. CPT Pharmacometrics Syst Pharmacol. 2022; 11(5):640-652.

59. Hendriksen LC, Omes-Smit G, Koch BCP, Ikram MA, Stricker BH,

Visser LE. Sex-based difference in the effect of metoprolol on heart rate and bradycardia in a population-based setting. J Pers Med. 2022; 12(6):870.

60. Füzi B, Malik-Sheriff RS, Manners EJ, Hermjakob H, Ecker GF. KNIME workflow for retrieving causal drug and protein interactions, building networks, and performing topological enrichment analysis demonstrated by a DILI case study. J Cheminform, 2022; 14(1):37.

61. Mohammadi Jouabadi S, Nekouei Shahraki M, Peymani P, Stricker BH, Ahmadizar F. Utilization of pharmacokinetic/pharmacodynamic modeling in pharmacoepidemiological studies: a systematic review on antiarrhythmic and glucose-lowering medicines. Front Pharmacol. 2022; 13:908538.

62. Niarakis A, Waltemath D, Glazier J, Schreiber F, Keating SM, Nickerson D, Chaouiya C, Siegel A, Noël V, Hermjakob H, Helikar T, Soliman S, Calzone L. Addressing barriers in comprehensiveness, accessibility, reusability, interoperability and reproducibility of computational models in systems biology. Brief Bioinform. 2022; 23(4):bbac212.

63. Heldring MM, Wijaya LS, Niemeijer M, Yang H, Lakhal T, Le Dévédec SE, van de Water B, Beltman JB. Model-based translation of DNA damage signaling dynamics across cell types. PLoS Comput Biol. 2022; 18(7):e1010264.

64. Pérez-Granado J, Piñero J, Medina-Rivera A, Furlong LI. Functional Genomics Analysis to Disentangle the Role of Genetic Variants in Major Depression. Genes (Basel). 2022; 13(7):1259.

65. Rodrigues D, van Kampen R, van Bodegraven AA, Kleinjans JCS, Jennen DGJ, de Kok TM. Gene expression responses reflecting 5-FU-induced toxicity: Comparison between patient colon tissue and 3D human colon organoids. Toxicol Lett. 2022; 371:17-24.

66. Trovato C, Mohr M, Schmidt F, Passini E, Rodriguez B. Cross clinical-experimental-computational qualification of in silico drug trials on human cardiac purkinje cells for proarrhythmia risk prediction. Front Toxicol. 2022; 4:992650.

67. Pérez-Granado J, Piñero J, Furlong LI. Benchmarking post-GWAS analysis tools in major depression: Challenges and implications. Front Genet. 2022; 13:1006903.

68. Jardi F, Kelly C, Teague C, Fowler-Williams H, Sevin DC, Rodrigues D, Jo H, Ferreira S, Herpers B, Van Heerden M, de Kok T, Pin C, Lynch A, Duckworth CA, De Jonghe S, Lammens L, Pritchard DM. Mouse organoids as an in vitro tool to study the in vivo intestinal response to cytotoxicants. Arch Toxicol. 2022; Online ahead of print.

69. González P, Prado-Rodriguez R, Gábor A, Saez-Rodriguez J, Banga JR, Doallo R. Parallel ant colony optimization for the training of cell signaling networks. Expert Syst. Appl. 2022; 208.

70. Mohr M, Chambard JM, Ballet V, Schmidt, F. Accurate in silico simulation of the rabbit Purkinje fiber electrophysiological assay to facilitate early pharmaceutical cardiosafety assessment: Dream or reality? J Pharmacol Toxicol Methods. 2022; 115: 107172.

IMPACT

on the European industry base

Impact

on the European industry base

In addition to the direct impact of the project in advancing toxicology modelling, TransQST has also contributed to the progress of the small and medium-sized enterprises (SMEs) that have either partnered in the project or have been born as a successful outcome of the same.

The consortium is proud to be part of these success stories, which highlight the importance of the Innovative Medicines Initiative funding scheme and the collaboration with industry through EFPIA as boosters of the European industry base of start-ups, entrepreneurs, innovators, and SMEs.

Acquisition of OcellO by CrownBio in 2021

After a thriving start as a provider of high-content imaging services and organoid-based modelling, TransQST partner OcellO was acquired by Crown Bioscience (CrownBio) in Summer 2021. CrownBio is a JSR Life Sciences global drug discovery and development service company, which provides translational platforms to advance oncology, immuno-oncology, and inflammatory disorders. The combined service portfolio of the companies was expanded by this union, OcellO providing expertise in high content imaging and CrownBio bringing in their advanced in vitro and in vivo screening and immunotherapy assessment services. The acquisition also contributed to the expansion of OcellO's facilities at their Leiden site both in lab space and access to recent technologies, as well as in terms of creating new jobs. The growth and success of OcellO are related to joint development of models to address specific project needs and the successes and scientific discoveries of other partners in TransQST. The consortium is glad to have contributed to this union which has allowed to make both companies stronger and more competitive.

SYNAPSE #1 SME in EU Health domain in Horizon 2020

TransQST managing partner Synapse gained the highest place in the podium as the number one SME in the EU health research projects since 2020, position which was maintained through the end of Horizon 2020 / IMI2.

TransQST has contributed to these excellent results by helping Synapse to leverage knowledge and lessons learned to related projects, as well by increasing the company´s visibility and contacts, therefore contributing to its future growth.

MBIS – start-up by TransQST Researchers

The DisGeNET knowledge management platform, available to all scientific community as an open-source tool, has been greatly enhanced during the project life. Based on the success of the platform, the TransQST IMIM researchers founded the spin-off company MedBioInformatic Solutions S.L. (MBIS) in 2020 to bring a commercial version of the platform to the market, under the name of DISGENET plus. TransQST has had an active participation in the further development of DisGeNET, providing it visibility both as an open-source tool to enhance biomedical research and as commercial solution for advanced use by the pharma sector in support of drug discovery.

TRANSQST

innovations acknowledged by
the EC Innovation Radar

TransQST

innovations acknowledged by the EC Innovation Radar

Another project impact that deserves a special mention is the recognition of TransQST innovations by the Innovation Radar, a European Commission initiative to identify high potential innovations and innovators in EU-funded research and innovation framework programmes.

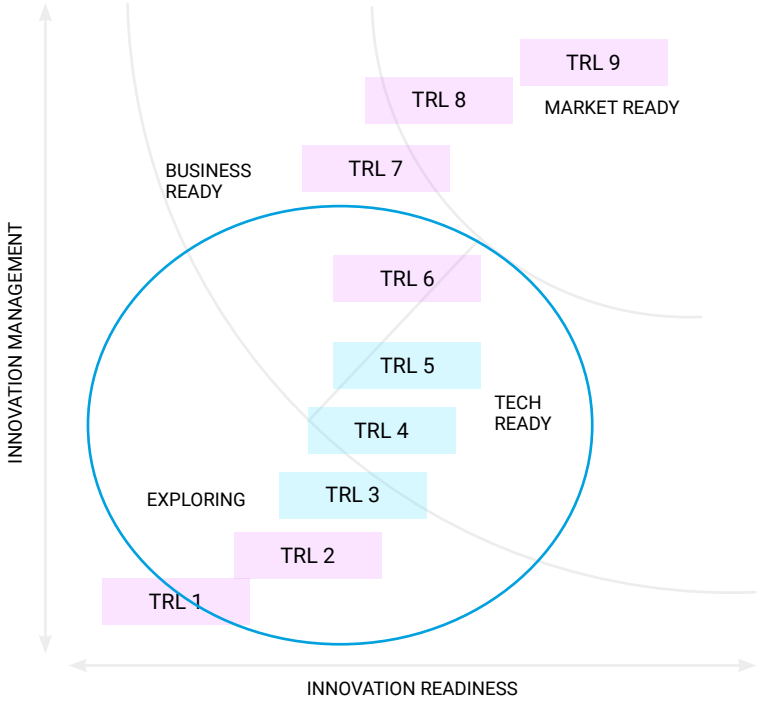
In Summer 2022, eleven innovations developed within TransQST were selected for their inclusion on the Innovation Radar platform as Exploring Innovations:
https://www.innoradar.eu/resultbykeyword/transqst

Exploring
Innovations actively exploring value creations opportunities

Tech Ready
Progressing on technology development process (e.g. pilots, prototypes, demostration)

Business Ready
Putting concrete market oriented ideas together (e.g. market studies, business plans, end-user engagement)

Market Ready
Outperforming in innovation management and innovation readiness. Considered "Ready for market"



These project innovations were included in the category of Good Health and Well-being[15], one of the United Nation´s 17 Sustainable Development Goals.

This acknowledgement by the Innovation Radar constitutes one of the project hallmarks, increasing the recognition of TransQST work across different audiences. Additionally, two of the innovations were especially highlighted by rating their market creation potential as Noteworthy.

The full list of accepted innovations is included in the below table 1.

TITLE	MATURITY LEVEL	KEY ORGANIZATIONS
DisGeNET: making disease genomics accessible for drug R&D	Exploring	IMIM / UPF (Universitat Pompeu Fabra) (part of eTRANSAFE project)
TXG-MAPr tools for improved detection of drug-induced toxicities	Exploring	UL / Eli-Lilly / AbbVie
BioModels Parameters: Precision data mining for model refinement	Exploring	EMBL- EBI
Modelling impact of toxicity in drug metabolising and eliminating organs on pharmacokinetics using physiologically based pharmacokinetic modelling	Exploring Market creation potential: Noteworthy	Certara

15 https://www.innoradar.eu/sdg/3

TITLE	MATURITY LEVEL	KEY ORGANIZATIONS
Mechanistic modelling of drug-induced Gastrointestinal epithelial injury to enable early prediction of clinical safety risk	Exploring Market creation potential: Noteworthy	AZ
Omnipath, a single access point to more than a hundred of intra- and intercellular signalling databases	Exploring	UKHD
Causal integration of multi-omics datasets	Exploring	UKHD
Logic modelling of intracellular signalling and drug effects	Exploring	UKHD
Hemodynamic simulator: Enabling cardiovascular modelling for safety pharmacologists	Exploring	UL
Systems model coupling physiologically-based pharmacokinetics and large-scale kinetic model of hepatic metabolism	Exploring	Certara
Causal network inference of signalling pathways from gene expression data	Exploring	UKHD