Newsletter Issue #1
December 2017
Translational quantitative systems toxicology to improve the understanding of the safety of medicines

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We are pleased to announce the launch of the **TransQST-Newsletter**, which aims to achieve a wider audience than the TransQST consortium members.

This Newsletter will be distributed twice yearly to briefly report on project news and achievements, from December 2017 to December 2021.

Project action fiche Visit our website

The ***Trans****lational* ***Q****uantitative* ***S****ystems* ***T****oxicology to improve the understanding of the safety of medicines* (TransQST) project is a 5-years IMI2 project that started in January 2017.

WHO we are Visit our website Consortium section

WHAT we do Visit our website Objectives section

- Build on existing PB-PK/PD models to define systemic as well as specific organ/cell exposure to drugs and metabolites in a holistic fashion.
- Develop SYSTEMS models for drug-induced organ damage across the four target organs (liver, kidney, cardiovascular and gastrointestinal-immune systems).
- Integrate PB-PK/PD models and output from SYSTEMS models into quantitative systems toxicology (QST) models.
- Test the models using selected compounds with nonclinical and human data.

WHY we do what we do

TransQST consortium research aims to give medicines developers more accurate and predictive decision-making tools for quantitative human drug safety assessment.

All activities in TransQST will be underpinned by a deep understanding of the physiological, pharmacological and toxicological relevance of data and models for predicting clinical adverse reactions. We are working to:

- Use pre-existing (and, where appropriate, *de novo*) 'omics data from fit-for-purpose nonclinical studies to identify Adverse Outcome Pathways for different toxicity endpoints, which will feed into new logic-based models of adverse reactions; and close apparent data gaps by dedicated experimentation and observation.
- Use network alignment algorithms, profiling tools and connectivity maps to provide a deeper understanding of species similarities and differences.
- Integrate enhanced PBPK models with network and systems biology models, at different levels or scale, to provide improved quantitative risk assessment for drug development.
- Identify novel safety biomarkers to improve physiological relevance of *in vitro* models of organ toxicity.
- Provide a more rational physiological basis for patient/volunteer selection during the design of clinical trials.
- Help to reduce significantly the animal usage by implementing the TransQST outcomes.
- Ensure that regulatory agencies (EMA, FDA) are engaged with the TransQST outcomes, collaborating to stablish bridges between innovative methodologies developers and regulators aiming safer medicines.

Project News Visit our website News section

Boehringer Ingelheim has joined the TransQST consortium, effective since July 2017. Their addition will complement and extend the coverage of the modelling framework within the particular area of GastroImmune toxicity assessment. Boehringer Ingelheim has become the 22nd partner of the TransQST consortium, with a contribution of 1,5M€.

2017 highlights. TransQST has finished the first year of the project life with several initial achievements that will facilitate to tackle the project goals.

- Based on existing data, a first list of **model compounds** for modelling challenges the target organs and systems (liver, kidney, cardiovascular and gastroimmune systems) was defined. To cover the lack of data in some cases, a gap analysis was carried out to define an **experimental plan**, and new data will be generated accordingly.

- The first release of the **data management platform** was launched, and this tool will give support for the integration of the data and the management of the knowledge related for the 4 target systems.
- The **Data Management Plan** has been defined based on all data types and their representation employed in toxicity modelling, with attention to the data standards and data/knowledge representation for their integration and use as input in the different modelling approaches.
- The **model selection process** and the **criteria for continuation or cessation of specific model development** among the project life were defined**.** In the case of cardiovascular system, the first work of modelling of potential anti-arrhythmogenic drugs on QTc prolongation and sudden cardiac death was reported to the consortium partners, and has been published in manuscript format.

Publications

Visit our website Publications section

Human *In Silico* Drug Trials Demonstrate Higher Accuracy than Animal Models in Predicting Clinical Pro-Arrhythmic Cardiotoxicity. Passini E, Britton OJ, Lu HR, Rohrbacher H, Hermans AN, Gallacher DJ, Greig RJH, Bueno-Orovio A, Rodriguez B. *Frontiers in Physiology*. 2017 Sept 12.

Partner involved: **UOXF.**

Integration of Genome Scale Metabolic Networks and gene regulation of metabolic enzymes with Physiologically Based Pharmacokinetics**.** Maldonado EM, Leoncikas V, Fisher CP, Moore JB, Plant NJ, Kierzek AM. *CPT Pharmacometrics Syst Pharmacol*. 2017 Aug 7.

Partner involved: **SIMCYP**.

Next issue in June 2018

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