Translational Quantitative Systems Toxicology (TransQST): Multi-Scale Modeling for Safety Assessment

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The philosophy underlying TransQST is that improved translation from nonclinical to human safety during clinical trials can be achieved with novel Quantitative Systems Toxicology models.

To achieve this goal, the TransQST partnership will:

- **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 four organs (Liver, Kidney, CV and GI systems).

- **Integrate** PB-PK/PD models and output from SYSTEMS models **into quantitative systems toxicology (QST) models**.

- **Test the models** using selected compounds with non-clinical and human data.

- **Form a unique and unprecedented public-private partnership** that leverages industry data and practical experience with public expertise in mechanistic work as well as modelling across scales of complexity.
- Develop an open (for consortium members), focused and **sustainable knowledge database** to build system toxicology models.

- Provide a clearer **understanding** of the translational confidence from non-clinical species to human.

- Support key risk assessment decisions, such as safety margin, clinical monitoring and reversibility, using mechanistic and quantitative modelling.

- Provide improved methods for visualising and analysing complex high content data to support drug safety assessment.

- Help inform regulatory decisions by providing evidence supporting the usefulness of QST modelling to support safety risk assessment.
Modeling Complex Systems
Multi-scale and multi-dimensional models of pathophysiology

Gene Expression Complexity
- multi-tissue Gx network
- intracellular Gx network
- intercellular Gx network

Dynamic Complexity (dose/time)

Gene
- stress response genes

Multi-TF Networks
- multi-TF Gx network

TF Network
- TF Gx network

Network
- L
- M
- H

Gene Expression Complexity
- proteolysis
- ROS

Organelle
- autophagy

Cell
- cell death

Biological Processes
- stellate/Kupffer cell activation
- cholestasis; fibrosis
- morbidity and mortality

Multicellular

Organ/Tissue

Organism

Pathophysiological Complexity

Multiple Transcriptomes

Transcriptome

Genes

Multicellular

Organ/Tissue

Organelle

Cell

Network

Gene

TF Network

Multi-TF Networks

Gene Expression Complexity

Modeling Complex Systems

Multi-scale and multi-dimensional models of pathophysiology

Pathophysiological Complexity

Stress response genes

proteolysis

ROS

Dynamic Complexity (dose/time)
Model biological systems as networks at a systems level.

Reduce dimensionality with ‘modular’ approaches.

Use pattern recognition to speed interpretation.

Interpret MOA in context of a systemic biological response.

Quantify translational risk (e.g. rat→man) using network preservation approaches.
Biological Systems are Modular Across Scales of Complexity

♦ **Modularity** refers to “…pattern[s] of connectedness in which elements of a system (e.g. mRNAs) are grouped into highly connected subsets” or modules.
  • Modules can be arranged in hierarchies based on loose connections between modules.

♦ Modular behavior can be captured in **unsupervised network** models using **coalescent properties** of the system.
  • Physical interactions – protein interaction networks
  • Dynamic interactions – gene regulatory networks
  • Statistical interactions – individual elements connected to phenotype

♦ **Co-regulation** in transcriptional networks is a **coalescent property** of biological systems – networks can self-assemble.
  • Connected at level of transcriptional control, e.g. Hox gene networks, Nrf2, etc.
  • Defined/modelled statistically to yield **co-expression modules**.

♦ Modeling complex systems as **networks of modules** has advantages:
  • Avoids the ‘curse of dimensionality.’
  • If 2X10⁴ genes form 2X10² modules complexity is reduced by 99%.
  • Biological content is retained.
  • Network visualization applied to modular systems improves data interpretation.
Co-expression modules (genes that respond similarly to drugs): 1 readout per module; the Eigengene (EiG).

WGCNA Test Dataset:
- Multiple drugs
- Multiple pathologies
- Multiple doses and time

WGCNA Build Dataset:
- Multiple drugs
- Multiple pathologies
- Multiple doses and time

9074 liver genes
The TXG_MAP: Linking gene network (modules) to pathogenesis.

Networks of co-expressing genes(modules)

DrugMatrix & TG-GATES (4182 treatments)

Relate networks to pathology (effect size)

LPS@1.25 mg/kd; 4hrs

Histopathology @ 4hr

VacuolationNOS:Hepatocellular
Mitosis_Increased:Hepatocellular
Infiltration|Inflammation:Inflammation
Hypertrophy:Hepatocellular
Hypertrophy-TG:Hepatocellular
Hyperplasia:Biliary
Hematopoiesis:Hematopoiesis
Glycogen_Increased:Hepatocellular
Fibrosis:Fibrosis
Dilation|Dilatation|Ectasia|Distension:...
Degeneration|Necrosis:hepatocellular
Hemorrhage|Edema: vascular
Apoptosis
Bortezimib
-0.3 ug/kg
-0.25d
GO-BP: (cellular) response to oxidative stress
GO-BP: fatty acid oxidation
GO-BP: cholesterol biosynthetic process
GO-CC: mitochondrion
GO-CC: endoplasmic reticulum
GO-CC: peroxisome

Fluvasatin
-94 mg/kg
-5d

Fenofibrate
-1000 mg/kg
-29d

BHA
-1000 mg/kg
-1d

BHA
-1000 mg/kg
-1d

Fluvasatin
-94 mg/kg
-5d

Eigengene Scores

Sutherland et al. The Pharmacogenomics Journal advance 2017
Location on the TXG_MAP for Modules that are Significant for Adverse Concurrent and Adverse@29d.

PANELS A and B: No adjustment for absAveEG to control for the high effect size for adverse concurrent and %DEG.
   a) Top-ranked modules selected for effect size >1.0 and p-value <10^{-17}
   b) Top-ranked modules selected for effect size >1.0 and p-value <10^{-5}
   c) This is outlined in detail in Fig 2 of Sutherland et al.

PANELS C and D: Modules with p-adjust values were selected to illustrate the effect of controlling for absAveEG as a covariate.
   a) Top-ranked modules selected for effect size >1.0 and p-adj <10^{-3}.
   b) Top-ranked modules selected for effect size >1.0 and p-adj <10^{-3}.
   c) This is outlined in detail in Fig 2 of Sutherland et al.
Model biological systems as networks at a systems level.

Reduce dimensionality with ‘modular’ approaches.

Use pattern recognition to speed interpretation.

Interpret MOA in context of a systemic biological response.

Quantify translational risk (e.g. rat→man) using network preservation approaches.
Role of JNK in APAP-Induced Liver Injury

JNK Activation Pathway

JNKs in TNF Signaling

Functions of JNKs in HCC
Increased cJun Binding After Bile Duct Ligation

(a) Percent change for select clinical chemistry endpoints.
(b) Severity scores for histology findings
(c) Scores for selected modules in ligated rats.
(d) TXG_MAP modules EG scores @1 day…
(e) …and 14 days
(f) ChIP-seq @ 1 and 14 day after ligation. Modules (>20 genes) are ordered by branch
Hierarchical clustering of 57 treatments from TG causing BDH in rats, using 415 co-expression modules, with treatment, dose in mg kg⁻¹ and days of dosing indicated on rows; four distinct subtypes were identified from the dendrogram.

- LEFT: Heatmap shows a subset of modules selected with recursive partitioning that recapitulate the (all-module) clustering and severity of liver histology findings.
- RIGHT: Heatmap on the right shows the histopathology scores for the same treatments.

*Abbreviations: bile duct ligation (BDL), 4,4’-methylenedianiline (MDA), 1-naphthyl isothiocyanate (ANIT), 2-acetylaminofluorene (2AAF), N-nitrosodiethylamine (DEN)
Comparison of BDH molecular subtypes in rats versus human liver disease.

<table>
<thead>
<tr>
<th></th>
<th>8</th>
<th>15m</th>
<th>37m</th>
<th>88</th>
<th>55m</th>
<th>39</th>
<th>2m</th>
<th>13m</th>
<th>23</th>
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<tbody>
<tr>
<td>sub-acute BDH (3-6 hours BDL)</td>
<td>0.0</td>
<td>-0.1</td>
<td>0.4</td>
<td>0.8</td>
<td>0.3</td>
<td>-0.1</td>
<td>0.0</td>
<td>0.0</td>
<td>0.3</td>
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<tr>
<td>acute BDH (0.5-3 days BDL)</td>
<td>0.5</td>
<td>0.0</td>
<td>0.9</td>
<td>3.4</td>
<td>2.6</td>
<td>0.7</td>
<td>0.9</td>
<td>-1.1</td>
<td>-0.8</td>
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<tr>
<td>chronic BDH (5-14 days BDL)</td>
<td>0.1</td>
<td>-0.8</td>
<td>1.0</td>
<td>3.2</td>
<td>3.5</td>
<td>3.3</td>
<td>2.2</td>
<td>-1.3</td>
<td>-1.4</td>
</tr>
<tr>
<td>BDH-carcinogens</td>
<td>1.3</td>
<td>1.5</td>
<td>1.5</td>
<td>2.9</td>
<td>3.1</td>
<td>1.5</td>
<td>1.2</td>
<td>-2.7</td>
<td>-2.6</td>
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<tr>
<td>type 2 diabetes (GSE23343)</td>
<td>0.1</td>
<td>-0.2</td>
<td>0.1</td>
<td>0.7</td>
<td>0.6</td>
<td>0.2</td>
<td>0.4</td>
<td>-0.5</td>
<td>-0.9</td>
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<td>normal liver from obese patients (GSE48452)</td>
<td>-1.4</td>
<td>-1.8</td>
<td>-0.7</td>
<td>-0.4</td>
<td>-0.2</td>
<td>0.1</td>
<td>2.0</td>
<td>0.2</td>
<td>-0.1</td>
</tr>
<tr>
<td>NAFL (GSE48452)</td>
<td>-1.8</td>
<td>-2.1</td>
<td>-1.1</td>
<td>-1.1</td>
<td>-0.4</td>
<td>-0.2</td>
<td>2.1</td>
<td>0.5</td>
<td>0.1</td>
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<tr>
<td>NASH (GSE48452)</td>
<td>-0.8</td>
<td>-1.7</td>
<td>1.0</td>
<td>1.1</td>
<td>1.1</td>
<td>1.9</td>
<td>2.2</td>
<td>-0.9</td>
<td>-0.4</td>
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<tr>
<td>biliary atresia (GSE46960)</td>
<td>-0.9</td>
<td>-1.1</td>
<td>0.4</td>
<td>1.5</td>
<td>1.2</td>
<td>3.0</td>
<td>1.0</td>
<td>-1.0</td>
<td>-1.7</td>
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<tr>
<td>acute liver failure, etiology HBV (GSE38941)</td>
<td>0.1</td>
<td>-0.8</td>
<td>1.4</td>
<td>1.0</td>
<td>3.0</td>
<td>5.3</td>
<td>4.5</td>
<td>-6.7</td>
<td>-10.2</td>
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<tr>
<td>alcoholic hepatitis (GSE28619)</td>
<td>1.4</td>
<td>1.1</td>
<td>1.5</td>
<td>3.1</td>
<td>2.4</td>
<td>3.1</td>
<td>0.9</td>
<td>-1.4</td>
<td>-0.6</td>
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<tr>
<td>cirrhosis adjacent to tumor, HCC, etiology HCV (GSE17856)</td>
<td>0.4</td>
<td>-0.4</td>
<td>1.4</td>
<td>0.7</td>
<td>1.7</td>
<td>1.1</td>
<td>1.8</td>
<td>-2.5</td>
<td>-2.1</td>
</tr>
<tr>
<td>HCC, etiology HCV (GSE17856)</td>
<td>2.9</td>
<td>1.5</td>
<td>4.9</td>
<td>-0.7</td>
<td>1.7</td>
<td>-2.8</td>
<td>-1.0</td>
<td>-6.3</td>
<td>-5.4</td>
</tr>
<tr>
<td>HCC, various etiologies (GSE62232)</td>
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<td>0.3</td>
<td>2.3</td>
<td>1.1</td>
<td>1.0</td>
<td>0.3</td>
<td>-0.3</td>
<td>-2.8</td>
<td>-3.2</td>
</tr>
<tr>
<td>Hepatoblastoma (GSE75271)</td>
<td>0.3</td>
<td>0.1</td>
<td>3.9</td>
<td>-1.1</td>
<td>-0.1</td>
<td>1.7</td>
<td>-0.7</td>
<td>-4.8</td>
<td>-9.7</td>
</tr>
</tbody>
</table>

Module scores are averaged across treatments in each BDH subtype (rats) from Figure 5 (top heatmap) and human samples (bottom heatmap) available in each Gene Expression Omnibus (GEO) series, identified via their accession number.
**HYPOTHESIS**: Probability of Human Liver Toxicity Given Nonclinical Toxicity is a Function of Network EiG, Preservation and Effect Size.

\[ p(hLT|rLT) = f(\text{networks}) \]
\[ p(hLT|rLT) = f(\text{EiG, eff size, preservation}) \]

Where:
- **EiG** – eigengene score (How much did it change?)
- **Eff Size** – Is the network associated with adverse outcomes?
- **Preservation** - Z-score (Is the network preserved in human?)
QUESTIONS?