10 YEARS OF BREAKTHROUGHS A HEALTHIER FUTURE

transQST

IMIM Parc de Salut MAR Barcelona — Institut Hospital del Mar d'Investigacions Mèdiques

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4

Network-based modeling of APAP-induced hepatotoxicity using interactomics and transcriptomics data

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Facts & Figures

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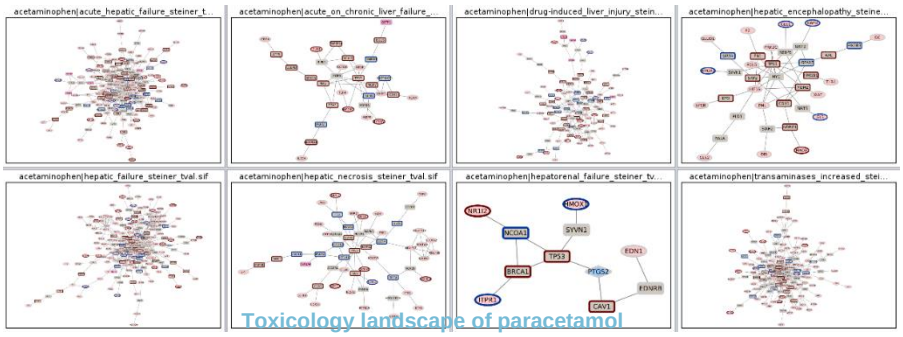
End date:	31/12/2021
Contributions	
IMI funding:	8 000 000 €
EFPIA in kind:	9 327 874 €
Total Cost:	17 327 874 €

Project website: transqst.org



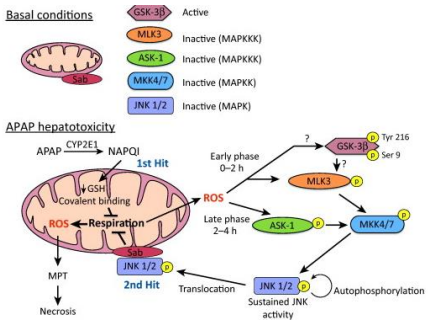
Toxicology landscape of paracetamol

Challenge

Paracetamol (acetaminophen, APAP) overdose alone is estimated to contribute around **40% of all acute liver failure cases** in the USA.

- The dose that induces hepatotoxicity in a person varies
- The intrinsic response to APAP differs across patients substantially

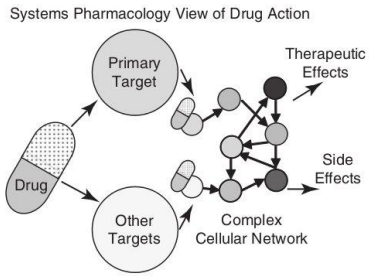
TransQST is an international effort to improve the understanding of the safety of medicines via translational quantitative systems toxicology. Within the context of **WP4** of TransQST, we aim to **model the APAP-induced toxicity** affecting liver using a systems biology approach.



Paracetamol-induced toxicity [1]

Approach & Methodology

We hypothesize that paracetamol induces a dose-dependent hepatotoxic response in the liver through the **perturbations of interactions** of the drug's off targets with toxicity-related proteins.



Drug action through off targets [2]

Problem formalization

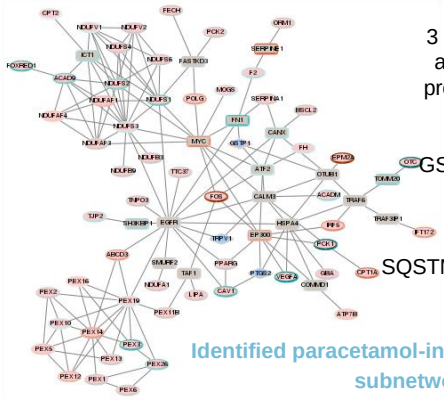
- Node-weighted Steiner tree that connects given seed nodes through other nodes ($S \in V'$)
- Minimizes the cost associated with including non-seed nodes ($\text{argmin}_{V'} |V'|$ & $\text{argmax}_{V'} |V' \cap T|$)
- Sets the costs such that drug response genes are easier to be included ($w_i = 10^{-|FC_i|}$)

Results

Adverse outcome phenotypes are manually curated from the literature (using LiverTox, MEDRA And DisGeNET), yielding eight adverse outcomes affecting human liver (see table).

Adverse outcome	# of genes
Acute hepatic failure	125
Acute on chronic liver failure	25
Drug-induced liver injury	86
Hepatic encephalopathy	31
Hepatic failure	173
Hepatic necrosis	35
Hepatorenal failure	5
Transaminases increased	99

Paracetamol-induced liver toxicity subnetwork is shown below. Nodes are highlighted based on APAP-induced gene expression (high dose, 24h, |FC| >1.5).



3 out of 9 APAP-targets are among 22 included proteins ($P = 1.1 \times 10^{-6}$)

- APAP targets: GSTP1, PTGS2, TRPV1
- De novo candidates: HSPA6, RELA, SFN, SQSTM1, TRIM55, TUBA1A

Identified paracetamol-induced liver toxicity subnetwork

Value of IMI collaboration

This work was possible due to a close collaboration and exchange of ideas as well as data between transQST partners. We especially thank Terezinha de Souza and Joaquim Aguirre-Plans for their help providing data.

Impact & take home message

- Interactome-based modeling offers systematic insights into APAP-induced hepatotoxicity
- The methodology can be seamlessly extended to other adverse outcomes

Data sets

- Liver-specific interactome data from InBioMap [3]
- Tissue expression for liver from GTEx (TPM > 1) [4]
- Adverse outcome associated genes (seeds) for DILI from DisGeNET based on LiverTox phenotypes [5]
- APAP targets from DrugBank
- APAP-induced gene expression (high dose, 24h from TG-GATES) [7]

References

[1] Han et al., 2013, Trends in Pharm. Sci.
[2] Berger and Iyengar, 2009, Bioinformatics
[3] Li et al., 2017, Nat Methods
[4] GTEx Consortium, 2013, Nat Genetics
[5] Piñero et al., 2016, NAR
[6] Wishart et al., 2017, NAR
[7] Igarashi et al., 2015, NAR

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