Designing physiological maps as a tool to study liver toxicology

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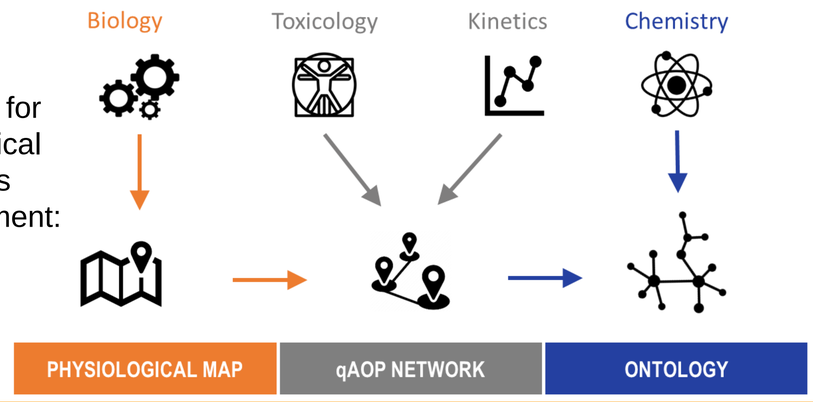
INTRODUCTION

Physiological Maps (PMs) are conceptual constructs that incorporate information as mechanistic representations of biological processes [1]. PMs can be used qualitatively and quantitatively as a mechanistic basis for improving Adverse Outcome Pathways (AOP) and supporting model rationale for several purposes.

Within the ONTOX project [1], we have created two PMs to study the following chemical-induced liver diseases: **Steatosis** and **Cholestasis**. The purpose of the PMs is to improve current **AOP networks** and develop **Ontologies** to support liver toxicity prediction.

Roadmap for Toxicological Ontologies establishment:

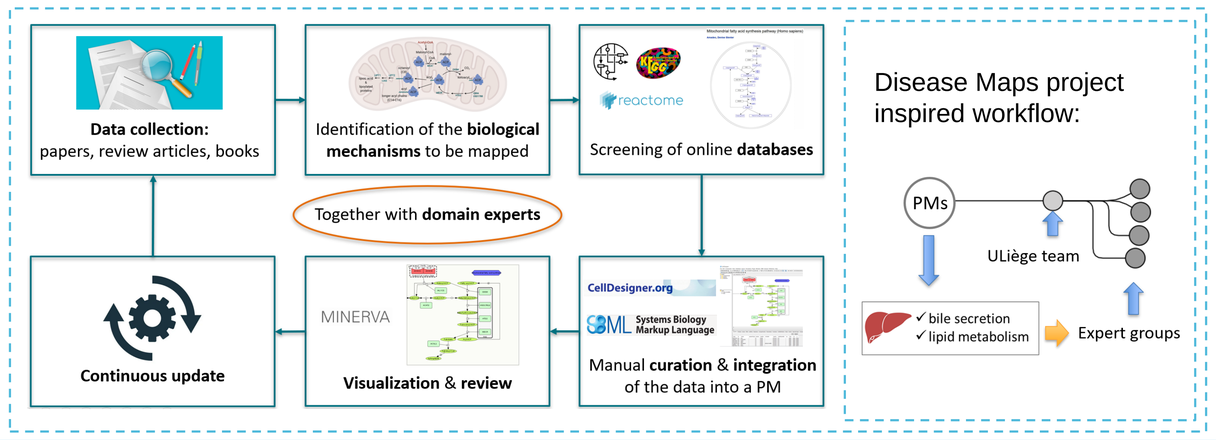


Scan to download the ONTOX inaugural paper [1].

METHODS

We adapted the workflow from the Disease Maps project [2] to construct our PMs.

- First, relevant physiological literature was curated with the help of domain experts.
- Next, we listed the fundamental mechanisms to be mapped and screened online databases (e.g. Wikipathways, Reactome, KEGG) for previously described pathways.
- Finally, we integrated pathways and data from the literature using the CellDesigner software and displayed them using the MINERVA platform [3].



RESULTS

Overview:

- Expert-curated maps;
- Human physiology-oriented networks;
- Qualitative and quantitative layers;
- Covers the current cholestasis AOP [4, 5];
- Covers the current steatosis AOP [6];
- Continuously updated.

Lipid Metabolism:

Key mechanisms described:

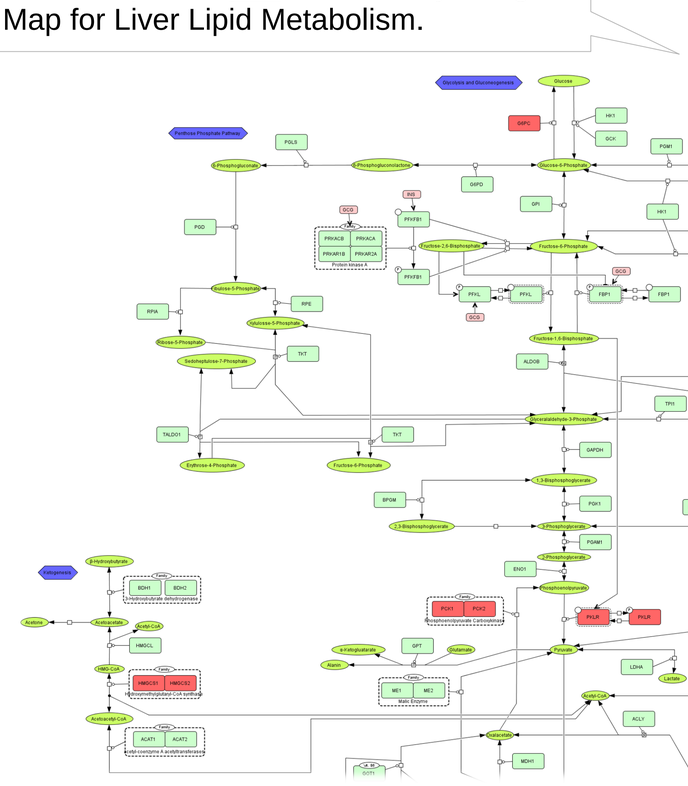
1. Fatty acids uptake;
2. Fatty acids synthesis;
3. Triacylglycerol synthesis;
4. Cholesterol synthesis;
5. Glycolysis;
6. Mitochondrial beta-oxidation;
7. Peroxisomal beta-oxidation;
8. Microsomal omega-oxidation;
9. Ketogenesis;
10. Very-low-density lipoproteins (VLDL) secretion;
11. Hormone regulation;
12. Transcriptional factors and nuclear receptor regulation.

Bile Acid Secretion and Metabolism:

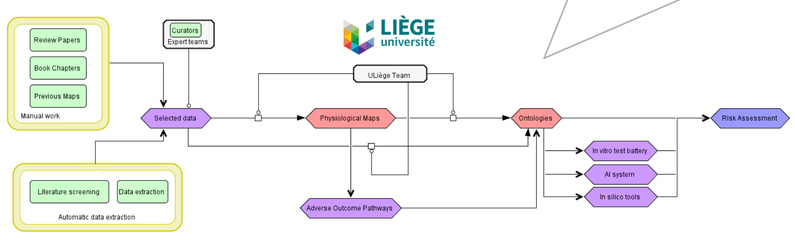
Key mechanisms described:

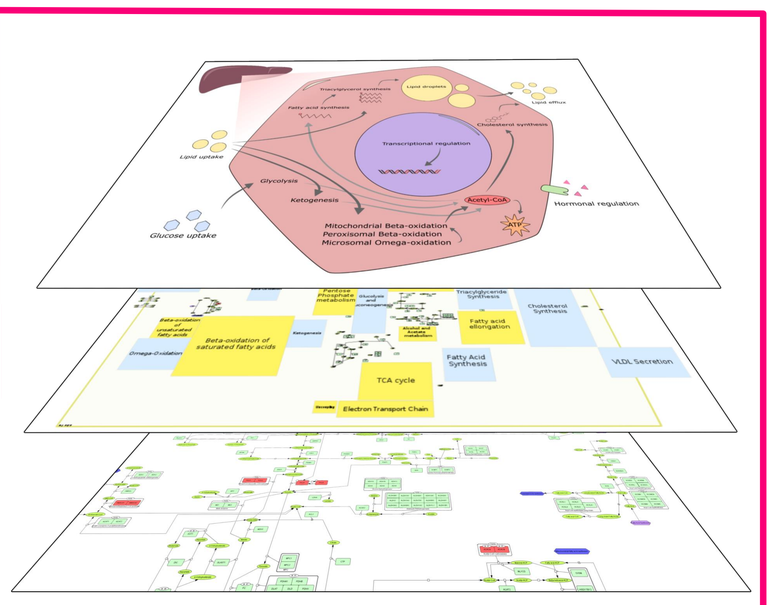
1. Bile acid synthesis,
2. Bile acid conjugation,
3. Bile acid secretion,
4. Ions exchange,
5. Bile formation and maturation,
6. Cholangiocytes secretion and absorption,
7. Bile acid reabsorption,
8. Bile acid recycling,
9. Hormones and transcriptional factors (as regulators).

An example of part of the Physiological Map for Liver Lipid Metabolism.



ULiège activities within the ONTOX workflow





Graphical concept of the ONTOX liver ontology

FUTURE STEPS

PMs are cornerstones to create **ontologies,** integrating different layers of pathological, toxicological, and chemical information, and quantitative kinetic data.

They will contribute to:

(1) better understand organ- and disease-specific pathways in response to chemicals;
(2) visualize omics datasets;
(3) develop quantitative methods for disease modelling and for predicting toxicity;
(4) set up an *in vitro* & *in silico* test battery to detect a specific type of toxicity;
(5) develop new **animal-free approaches** for **next generation risk assessment**.

These tools will be continuously updated, resulting from expert curation and revision in an open community effort.

References: [1] Vinken, M. et al. 2021 - 10.1016/j.tox.2021.152846. [2] Mazein, A. et al. 2018 - 10.1038/s41540-018-0059-y. [3] Hoksza, D. et al. 2019) - 10.1093/bib/bbz067. [4] Vinken, M. et al. 2013 - 10.1093/toxsci/kft177. [5] Gijbels, E. et al. 2020 - 10.1007/s00204-020-02691-9. [6] Mellor, Claire L., et al. 2016 - 10.3109/10408444.2015.1089471.

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