

Physiology-based framework to study chemical-induced cholestasis



Luiz Carlos Maia Ladeira¹, Alessio Gamba¹, Raphaëlle Lesage², Jonas van Ertvelde³, Jian Jiang³, Anouk Verhoeven³, Daniël Roodzant⁴, Marc Teunis⁴, Ramiro Jover⁵, Tamara Vanhaecke³, Mathieu Vinken³, Liesbet Geris^{1,2,6}, Bernard Staumont¹

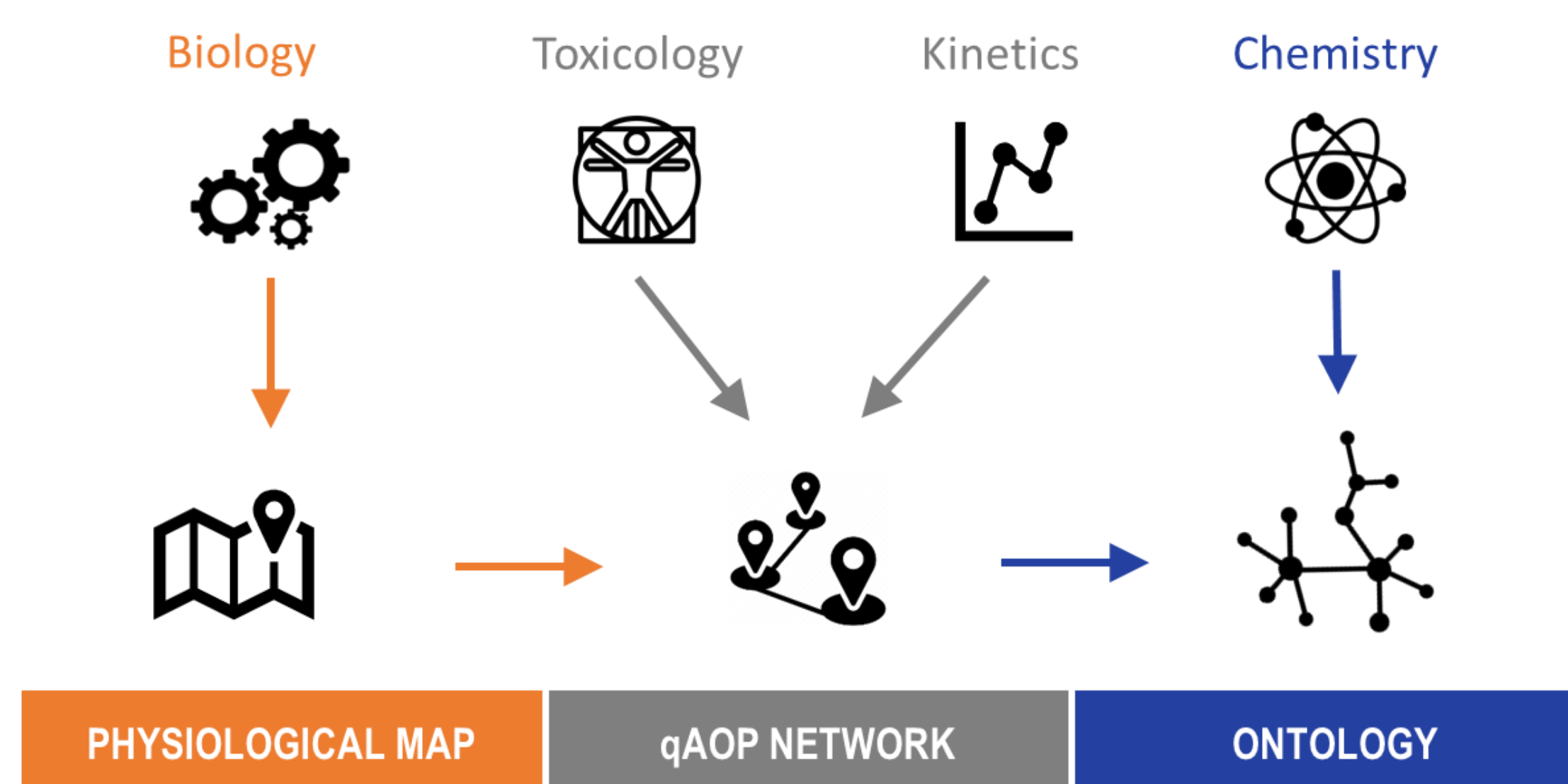
¹Biomechanics Research Unit, GIGA In Silico Medicine, University of Liège, Belgium; ²Skeletal Biology and Engineering Research Center, KU Leuven, Belgium; ³Department of In Vitro Toxicology and Dermato-cosmetology, Vrije Universiteit Brussel, Belgium; ⁴Innovative Testing in Life Sciences & Chemistry, University of Applied Sciences Utrecht, The Netherlands; ⁵Dept. Biochemistry, University of Valencia, IIS Hosp. La Fe, CIBERehd, Spain; ⁶Biomechanics Section, Department of Mechanical Engineering, KU Leuven, Belgium.

Introduction

Physiological Maps (PMs) are conceptual constructs that integrate knowledge as mechanistic representations of biological processes [1]. PMs can be used qualitatively and quantitatively as a mechanistic background in Adverse Outcome Pathways (AOP) creation and refinement, supporting model rationale, and to develop computational models serving different purposes.

Here, we developed a bile secretion and metabolism PM to serve as a framework to improve a cholestasis AOP network and build an **ontology** [1] for the study of chemical-induced cholestasis.

Roadmap for the establishment of toxicological ontologies:



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, exported as [SBML](#) (Systems Biology Markup Language) and displayed them using the [MINERVA](#) platform [3].

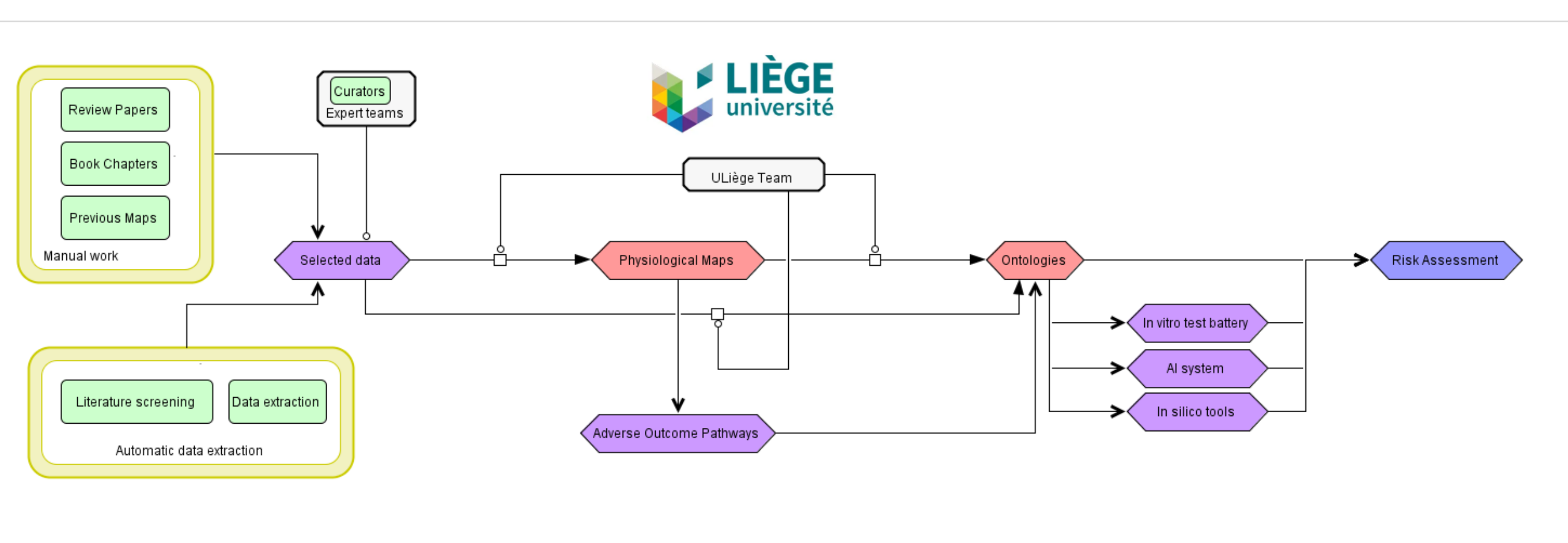
Results

- Expert-curated;
- Human physiology-oriented network;
- Qualitative and Quantitative layers;
- Covers the current cholestasis AOP [4, 5];
- Continuously updated.

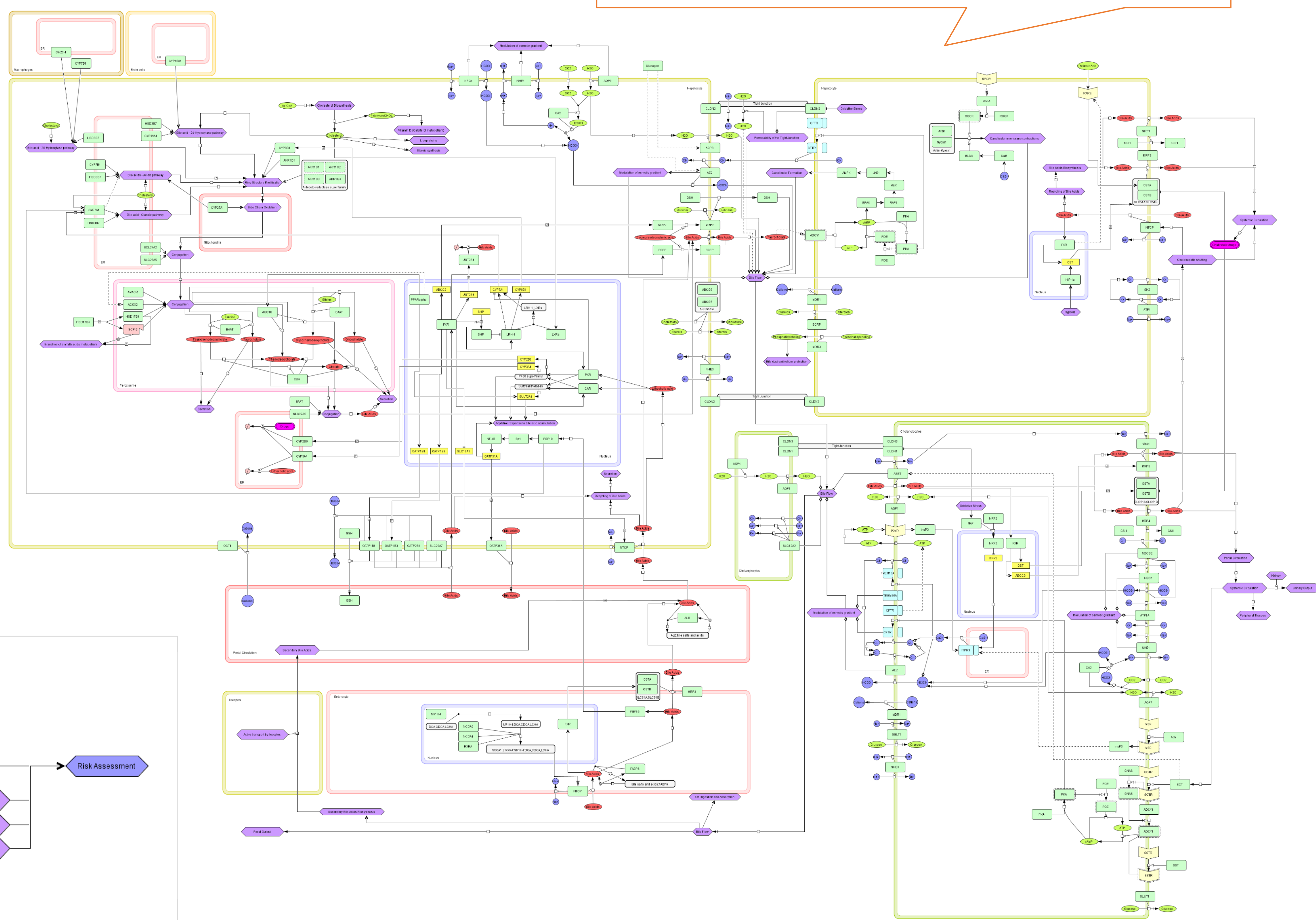
- Key mechanisms described:

- Bile acid synthesis,
- Bile acid conjugation,
- Bile acid secretion,
- Ions exchange,
- Bile formation and maturation,
- Cholangiocytes secretion and absorption,
- Bile acid reabsorption,
- Bile acid recycling,
- Hormones and transcriptional factors (as regulators).

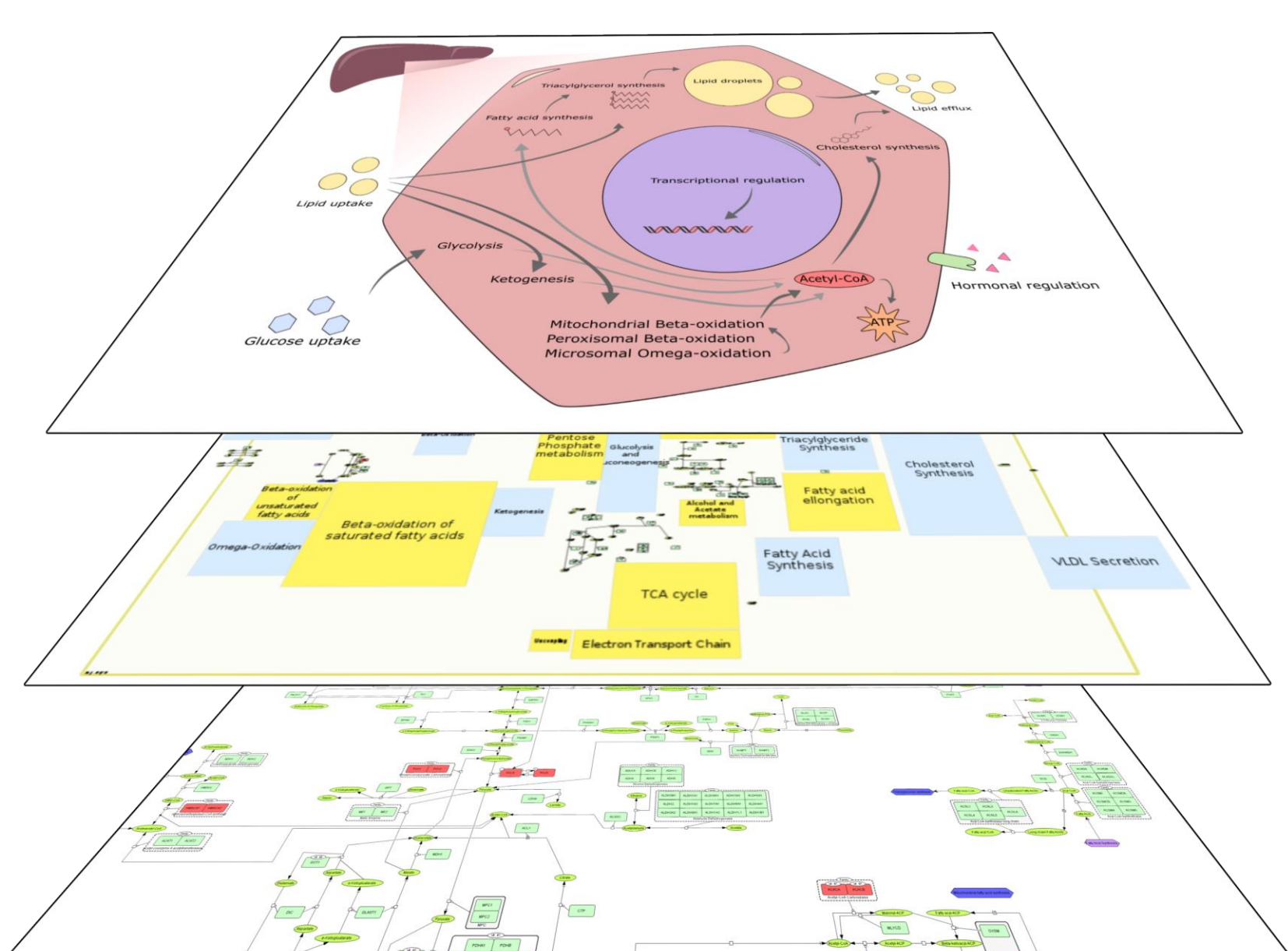
ULiège activities within the ONTOX workflow



The Physiological Map for Bile Secretion and Metabolism



Future steps



Graphical concept of the ONTOX liver ontology

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

They will contribute to:

- better understand organ- and disease-specific pathways in response to chemicals;
- visualize omics datasets;
- develop quantitative methods for disease modelling and for predicting toxicity;
- set up an *in vitro* & *in silico* test battery to detect a specific type of toxicity;
- 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](#).
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Further information:

lcadeira@uliege.be
B.Staumont@uliege.be
Liesbet.Geris@uliege.be

<https://ontox-project.eu/>

