Bile Secretion Physiological Map and the Cholestasis Ontology
as innovative tools for understanding the mechanisms of cholestatic liver disorders

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The **Bile Secretion Physiological Map** (BSPM) and the **Cholestasis Ontology** are valuable resources for the ONTOX [Vinken et al, 2021] project's goal of developing **new approach methodologies** for next generation risk assessment (NGRA) of chemicals and disease modelling. The BSPM provides a comprehensive overview of the cellular and molecular processes involved in bile acid production and secretion in the liver and serves as a foundation for developing and refining adverse outcome pathways for cholestasis. The **Cholestasis Ontology**, on the other hand, integrates different layers of pathological and toxicological information, chemical, and kinetic data to provide a multi-layered platform for understanding organ/disease-related pathways in response to chemicals.

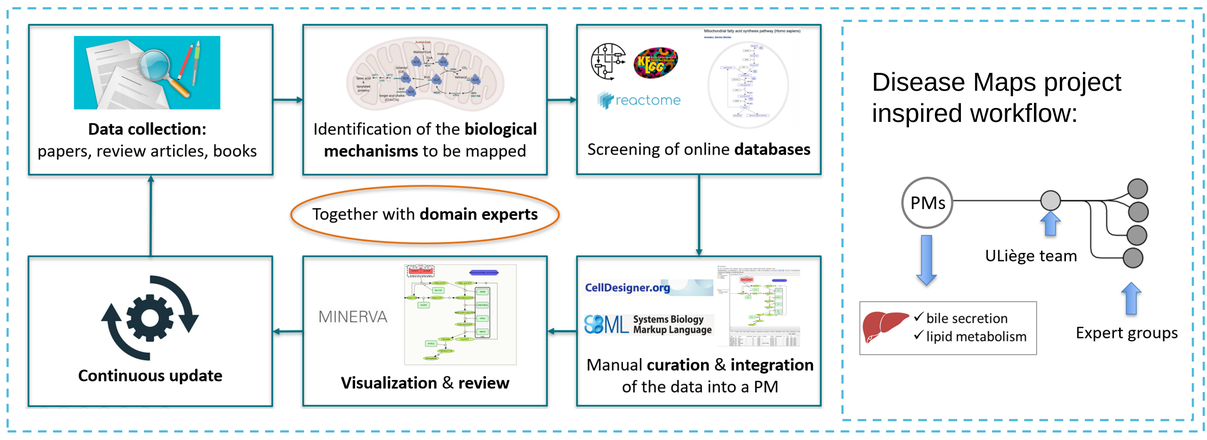
The applications of the BSPM and the Cholestasis Ontology are diverse, including setting up *in vitro* and *in silico* test batteries. These resources can also aid in the development of new drug therapies and personalized medicine by visualizing omics datasets and extracting information from network analysis. Furthermore, the BSPM and the Cholestasis Ontology can help reduce the use of animals in research.

In summary, the BSPM and the Cholestasis Ontology developed in the ONTOX project are versatile assets for expanding toxicological knowledge and developing NGRA approaches. They can help to better understand the mechanisms of bile acid secretion and cholestasis and provide valuable insights into the effects of chemicals on human health.

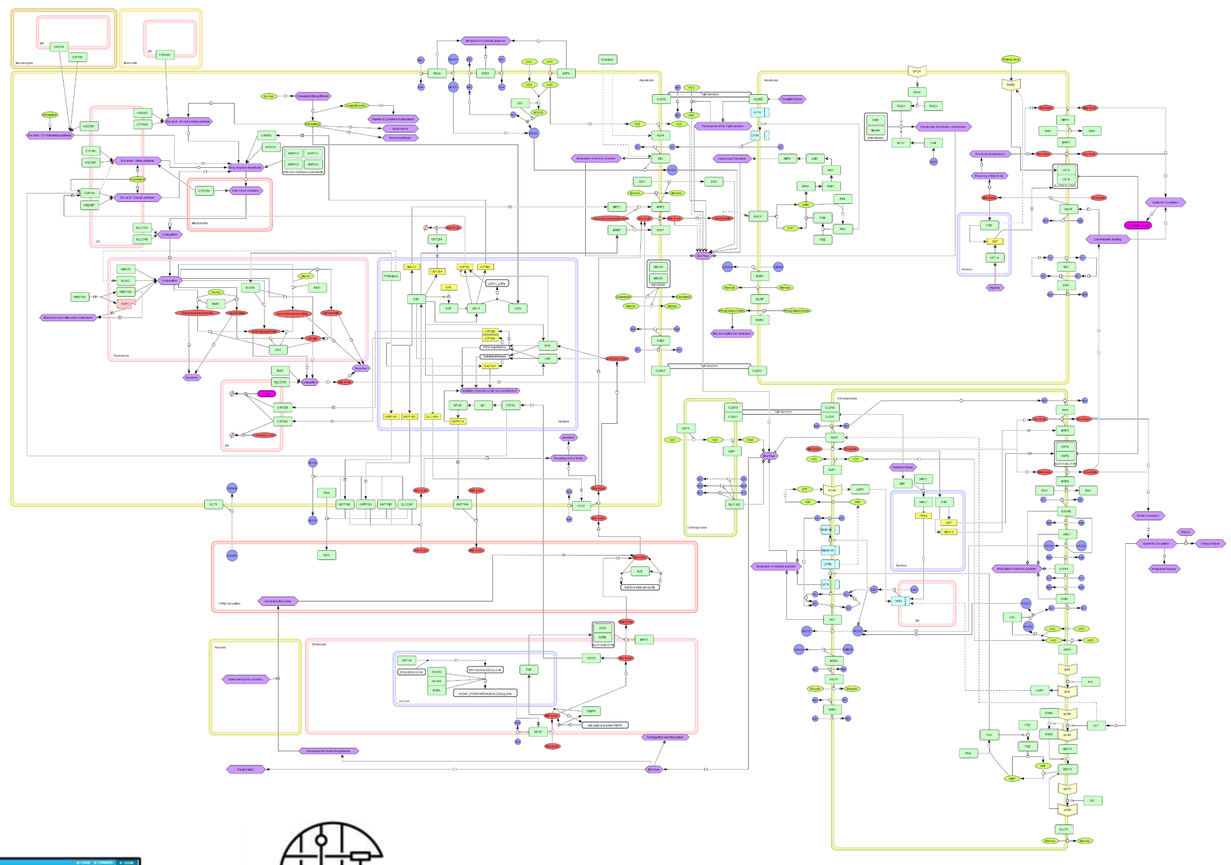
Methods

We adapted the workflow from the Disease Maps project [Mazein et al, 2018] to construct our physiological maps. The Ontology is created by the integration of chemical, pathological and kinetic data on the map.

- 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 [Hoksza et al, 2019].



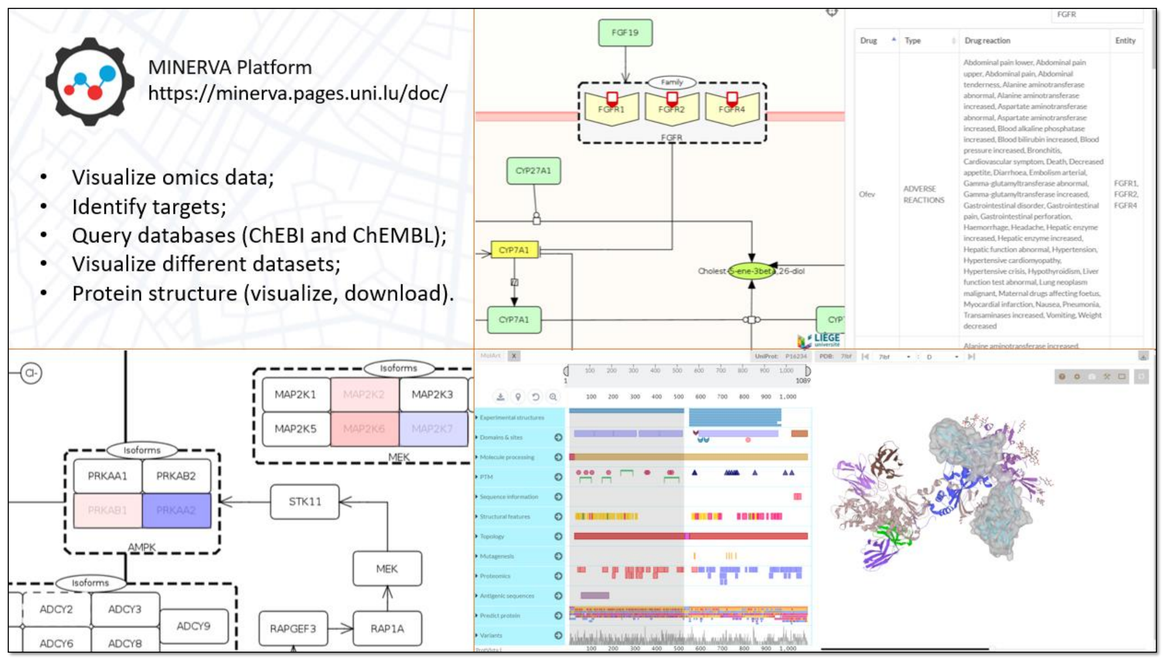
Physiological Map



Applications

MINERVA Platform
https://minerva.pages.uni.lu/doc/

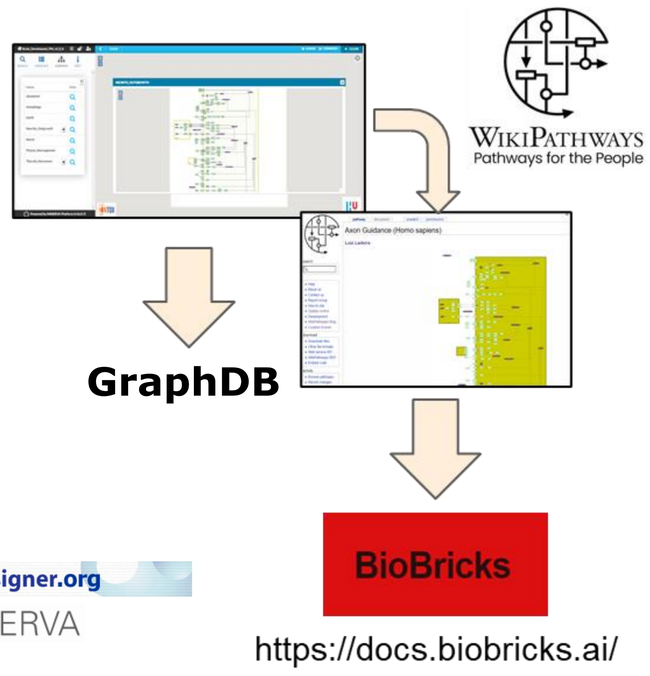
- Visualize omics data;
- Identify targets;
- Query databases (ChEBI and ChEMBL);
- Visualize different datasets;
- Protein structure (visualize, download).



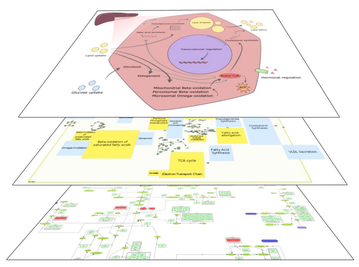
Perspectives

(1) Use the ontologies to better understand organ- and disease-specific pathways in response to chemicals;
(2) Develop quantitative methods for disease modelling and for predicting toxicity;
(3) Automate the map construction using AI tools;
(4) Integrate the ontologies into the other databases to assist mechanistic risk assessment;
(5) Set up an *in vitro* & *in silico* test battery to detect a specific type of toxicities;
(6) 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.



sysrev → SBtab → Phymdos → SBML
https://sysrev.com/
CellDesigner.org
MINERVA



Graphical concept of the ONTOX ontology: a multilayer tool integrating biological, chemical, toxicological and kinetic data.

Physiological Map was built using the CellDesigner software - https://www.celldesigner.org/

Visualization and exploration powered by the MINERVA platform - https://minerva.pages.uni.lu/

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https://ontox-project.eu/

References: Vinken, M. et al. 2021 - 10.1016/j.tox.2021.152846. Mazein, A. et al. 2018 - 10.1038/s41540-018-0059-y. Hoksza, D. et al. 2019 - 10.1093/bib/bbz067.

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