In silico approaches in organ toxicity hazard assessment: current status and future needs

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- Overview of the project
- General strategy
- Liver toxicity
- Challenges and further research

Overview of the project

To create *in silico* protocols for hazard assessment of major toxicological endpoints, similar to test guidelines routinely used in the application of *in vitro* or *in vivo* methods

Over 60 international organizations | NIH grant | **Led by Leadscope, Inc.**

Publication of frameworks for performing such an assessment

2018

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In silico toxicology protocols

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Genetic toxicology *in silico* protocol☆

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2020

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Skin sensitization *in silico* protocol

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Protocols vs. position papers (review of state-of-the-art) for complex endpoints such as: **organ toxicity (cardiac, liver, renal, pulmonary)**

Other endpoints to be soon completed:
acute oral toxicity (protocol), neurotoxicity (position paper), carcinogenicity (position paper)

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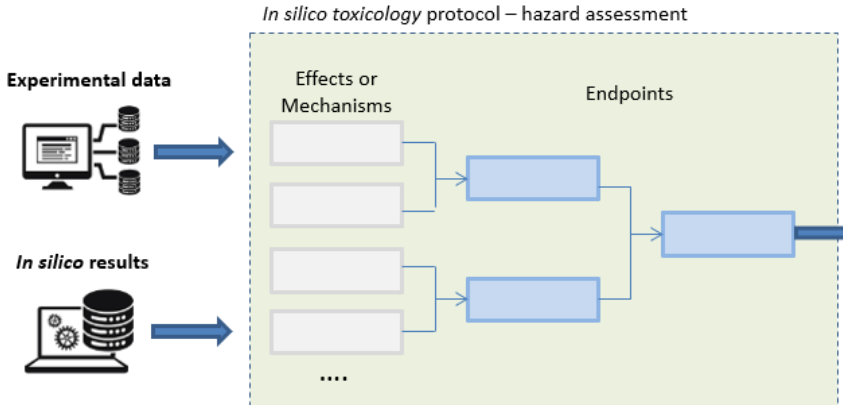
Overview of the project

General strategy

Liver toxicity

Challenges and further research

In silico toxicology protocols: general strategy

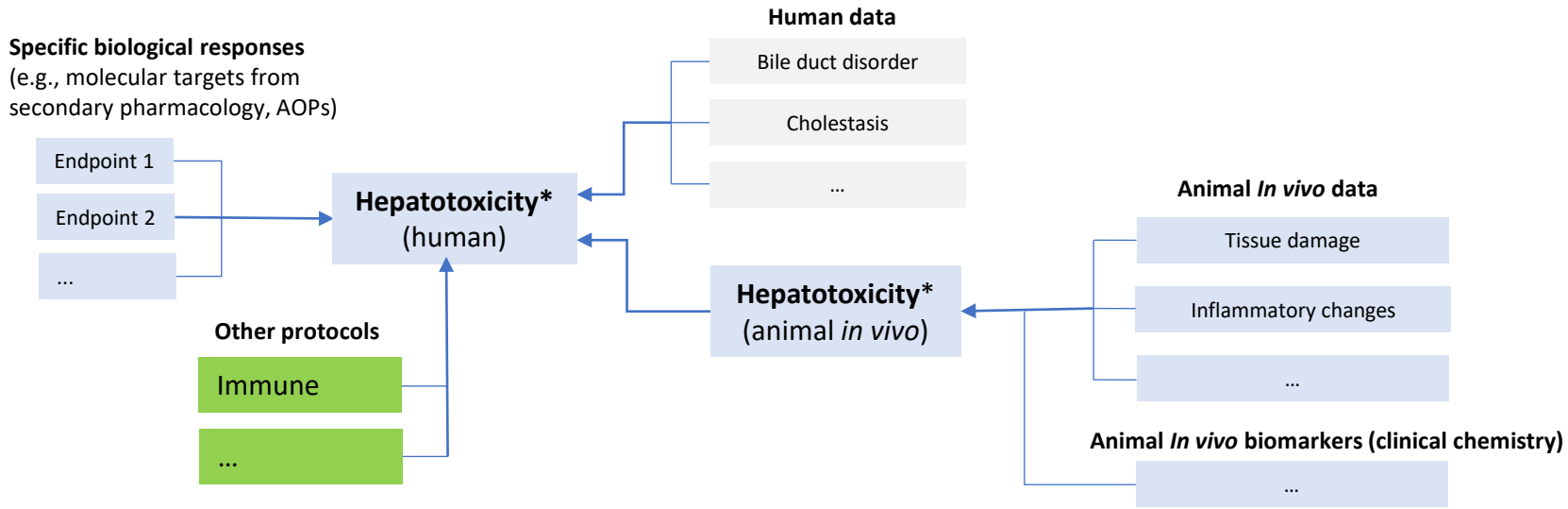


Definition of in silico/models and experimental data for each effect/mechanism

Rules/principles for combining information

Guidelines (e.g. expert review)

Liver toxicity: draft assessment framework



** Dose, duration, based on experimental and/or in silico results*

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General strategy

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Challenges and further research

Challenges and further research

Importance of mechanistically-driven approach

Many biological pathways → Many endpoints → Development of predictive in silico mechanistically-informed models is challenging

Limitation of tests (e.g., in vitro assays for MIEs/KEs)

Lack of large in vivo databases
(1. chemical structures 2. annotations
3. POS & NEG results, timepoints, concentrations)

Ontology

Limited in silico models predicting dose/timepoints - mainly classification models

Ordinal models, Read-across

Importance of internal exposure and ADME processes, e.g. reactive metabolites

Key characteristics of toxicants to a specific target organ, similar to the ten key characteristics of carcinogens

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