CEFIC Long-range Research Initiative
Request for Proposals (RfP)

Title and Code Number:
LRI-AIMT5: Towards Building an AOP Prenatal Developmental Toxicity Ontology

Background
Current safety testing does not exploit state of the science. The data and information explosion in developmental biology and toxicology over the last few years has made it necessary to organize the information in the field of toxicology in a different way. These data come from high-throughput (HTP) assay batteries, global gene expression studies, and other sources that rely on harnessing biotechnology to provide information on chemical interactions with biological systems at basic levels of biological organization, as well as HTP methods for assessing the effects of chemicals on the development of model organisms such as zebrafish. In particular, the increasing amounts of data that inform us about molecular pathogenesis leading to human developmental toxicity, now motivate the implementation of human developmental toxicity Ontology.

Such an Ontology will inform the elucidation of AOPs relevant to systems toxicology and predictive toxicology for prenatal and neonatal life (Villeneuve reviews, Wu et al); help in the identification of mechanistically-based biomarkers and serve as a platform for systems toxicology for prenatal development (Sturla et al, 2014). It will also help guide the design of chemicals without evident potential for developmental toxicity.

Objectives
This project will develop a formal system (ontology) that organizes the knowledge of chemical structure and developmental biology to predict and explain which chemicals will induce human developmental toxicity.

The projects objectives are to:

1. Incorporate information at a variety of levels of biological organization, including but not limited to molecular targets and molecular initiating events and their associated chemistries. For example, one can identify chemical features that support binding to specific receptors or enzymes, or electrophilic attack of macromolecules.

2. Comprehensively cover initial molecular interactions and downstream consequences using available information on the chemistry and biology shown to invoke developmental toxicity.

3. Link biochemical changes, cellular consequences, embryological events, and developmental processes with enough specificity to support the formulation of hypotheses about the pathways leading from initial chemical interaction to specific adverse outcomes.

4. Link with existing ontologies including those describing developmental processes and defects, where possible, to ensure interoperability (e.g OECD AOP- wiki).

5. Enable the toxicology community to develop computational approaches and be compliant with open standards for ontologies (e.g. OWL) and systems biology (e.g. SBML). However it will also be user-friendly such that it is accessible and useable by the computer non-specialist.

Scope

The proposed ontology aims to formalize a system that integrates 'vertical' classification of adverse developmental outcomes (e.g. apical endpoints in a prenatal developmental toxicity animal study) with 'horizontal' classifications (in which the developmental lineages, spatial dynamics and staging of critical transitions leading to adverse outcomes can be derived from the expanding knowledge base of developmental biology, particularly from small model organisms and animal models of human disease).

This will be a toxicology-driven effort in collaboration with developmental biologists, toxicologists and ontologists. The investigators should consider data that is available in the peer reviewed literature as well as freely accessible data sources such as ToxCast; public repositories of gene expression information; compilations of toxicology data organised by chemical structure (e.g. ACToR, DSSTox); and previously developed ontologies - particularly those for developmental biology. See 'references' below for an additional source of information.

<u>Knowledge Gaps to be addressed by the project:</u>

- AOPs based on current knowledge are likely to have many gaps (whilst there are ontologies describing normal and abnormal developmental outcome, there are not ontologies for chemical/molecular interaction/MOA). Therefore, this research project aims to support AOP development by systematising information where it is strongest and best developed (at the level of adverse outcome and chemical/molecular interaction/mode of action) providing a strong foundation for future AOP development.

- Connect new data streams at the chemical and biomolecular levels with traditional toxicity data at the organ/organismal levels.

- Organize growing volume and diversity of data and information in developmental biology and toxicology in an integrated manner that enables computational approaches.

The final report shall contain an executive summary (2 pages max), a main part (max. 50 pages) and a detailed bibliography. It is expected that the findings will be developed into at least one peer reviewed publication, following postering(s) and presentation(s) at suitable scientific conference(s).

Cost and Timing
Start in September 2015, duration 2 years
Budget in the order of €300.000

Partnering/Co-funding
Applicants should provide an indication of additional partners and funding opportunities that can be appropriately leveraged as part of their proposal. Partners can include, but are not limited to industry, government/regulatory organizations, research institutes, etc. Statements from potential partners should be included in the proposal package. Synergies across related activities will be pursued as appropriate, for example ongoing work in the ToxCast / Tox21, WHO and specifically OECD.

Fit with LRI objectives/Possible regulatory and policy impact involvements/ Dissemination
Applicants should provide information on the fit of their proposal with LRI objectives and an indication on how and where they could play a role in the regulatory and policy areas. Dissemination plans should also be laid down.

References

For the developmental biology aspect of the ontology, useful web-links include:

ICD-9-CM codes (WHO): http://wwwgov.cdc./nchs/icd/icd9cm.htm
OWL website http://www.w3.org/TR/owl-guide/
BioPortal website http://bioportal.bioontology.org/
Devtox.org: http://devtox.org/
EMAP website: http: //www.emouseatlas.org/emap/home.html
ZFIN resource: http://zfin.org/
Jackson Labs database (MPO browser, MGI): http://www.informatics.jax.org/
http://www.embrys.jp/embrys/

For organising toxicology information, useful references include:

Framework for identifying chemicals with structural features associated with the potential to act as developmental or reproductive toxicants. Wu S, Fisher J, Naciff J, Laufersweiler M, Lester C, Daston G, Blackburn K.Chem Res Toxicol. 2013 Dec 16;26(12):1840-61. doi: 10.1021/tx400226u

Systems toxicology: from basic research to risk assessment. Sturla SJ, Boobis AR, FitzGerald RE, Hoeng J, Kavlock RJ, Schirmer K, Whelan M, Wilks MF, Peitsch MC. Chem Res Toxicol. 2014 Mar 17;27(3):314-29. doi: 10.1021/tx400410s.

Villeneuve D.L., Crump, D., Garcia-Reyero N., Hecker, M., Hutchinson, T.H., LaLone,

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C.A., Landesmann, B., Lettieri, T., Munn, S., Nepeska, M., Ottinger, M.A., Vergauwen, L. Whelan, M. (2014) Adverse Outcome Pathway Development I: Strategies and Principles. Toxicological Sciences, 142(2), 2014, 312-320

Villeneuve D.L., Crump, D., Garcia-Reyero N., Hecker, M., Hutchinson, T.H., LaLone, C.A., Landesmann, B., Lettieri, T., Munn, S., Nepeska, M., Ottinger, M.A., Vergauwen, L. Whelan, M. (2014) Adverse Outcome Pathway Development II: Best Practices. Toxicological Sciences, 142(2), 2014, 321-330.

DEADLINE FOR SUBMISSIONS: 6 Sept 2015

Please see www.cefic-lri.org for general LRI objectives information, project proposal form and further guidance for grant applications.