



# Introducing WikiPathways to support Adverse Outcome Pathways for regulatory risk assessment

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## Introduction

Regulatory toxicology needs reliable, efficient, animal-free methods to perform risk assessment of chemicals and nanomaterials, [1] such as omics technologies. [2,3] The gap between these molecular-level measurements and risk assessment can be bridged by the Adverse Outcome Pathways (AOPs). [1,4] Although omics-based approaches have become valuable tools in toxicological research [2,3], the implementation in the AOPs and acceptance by the risk assessment community is challenging. [5] Besides, the current infrastructure for AOPs does not allow the integration of omics technologies. Here we show how WikiPathways [6] can support the integration of omics technologies with AOPs and allow the analysis and interpretation of omics datasets. (Figure 1)

## Methods/Objective

The AOP Wiki XML was downloaded and parsed, extracting stressor information, ontology annotations, and information on Key Events and Key Event Relationships. Stressor chemicals CAS numbers were mapped to ChEBI using BridgeDB. [7] Gene and proteins were extracted using human HGNC gene symbols. The WikiPathways SPARQL endpoint was used to extract the ontology use, retrieve pathways by gene lists and search for chemicals. Manual validation was performed.

## Results

The semantic annotations of AOP Wiki and WikiPathways do not currently allow integration due to differences in the vocabularies and types of information that is annotated. (Figure 2) Automated linkage of identifiers indicated that 30% of AOP Wiki chemicals were found in WikiPathways, while genes extracted from Key Events and Key Event Relationships showed an overlap of 70% and 71%, respectively. (Figure 3) Manual matching of Key Events indicated that 67% can be linked with molecular pathways on WikiPathways. (Figure 4)

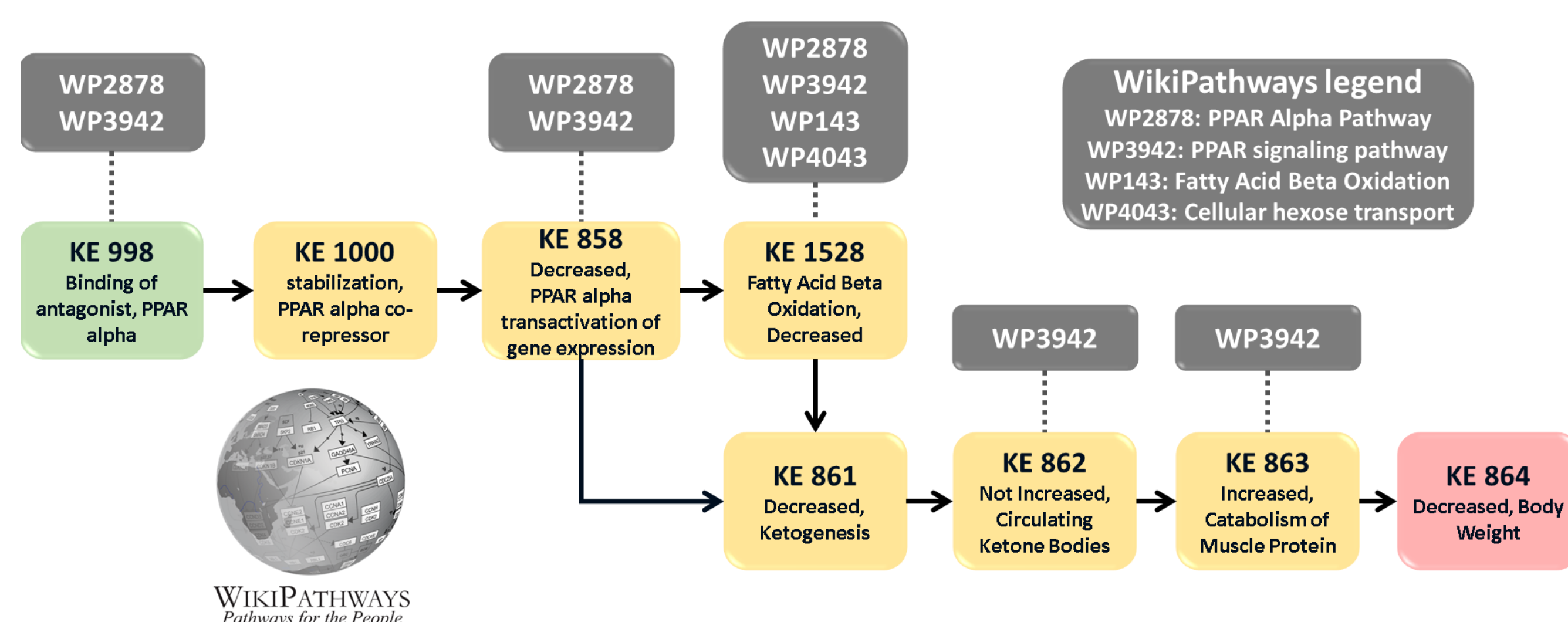


Figure 4: An example AOP from AOP Wiki (AOP 6) that is connected to molecular pathways in WikiPathways by manual matching. WP: WikiPathways, KE: Key Event

## Conclusion

We believe that the integration of AOP Wiki with WikiPathways will improve risk assessment by allowing direct linkage of omics data to Key Events. However, major changes are needed in both WikiPathways and AOP Wiki to make the assessment reproducible and valid. There are many opportunities to create more direct connections from the AOP Wiki through extended ontology annotations and usage of identifiers, improving interoperability of the database, and by allowing the regulatory toxicology community to contribute through the AOP Portal on WikiPathways. [8]

## Objective

Our objective was to identify the existing implementations of semantic annotations by the AOP Wiki, such as ontologies, and identifiers for genes, proteins or metabolites, and use these to connect it to WikiPathways.

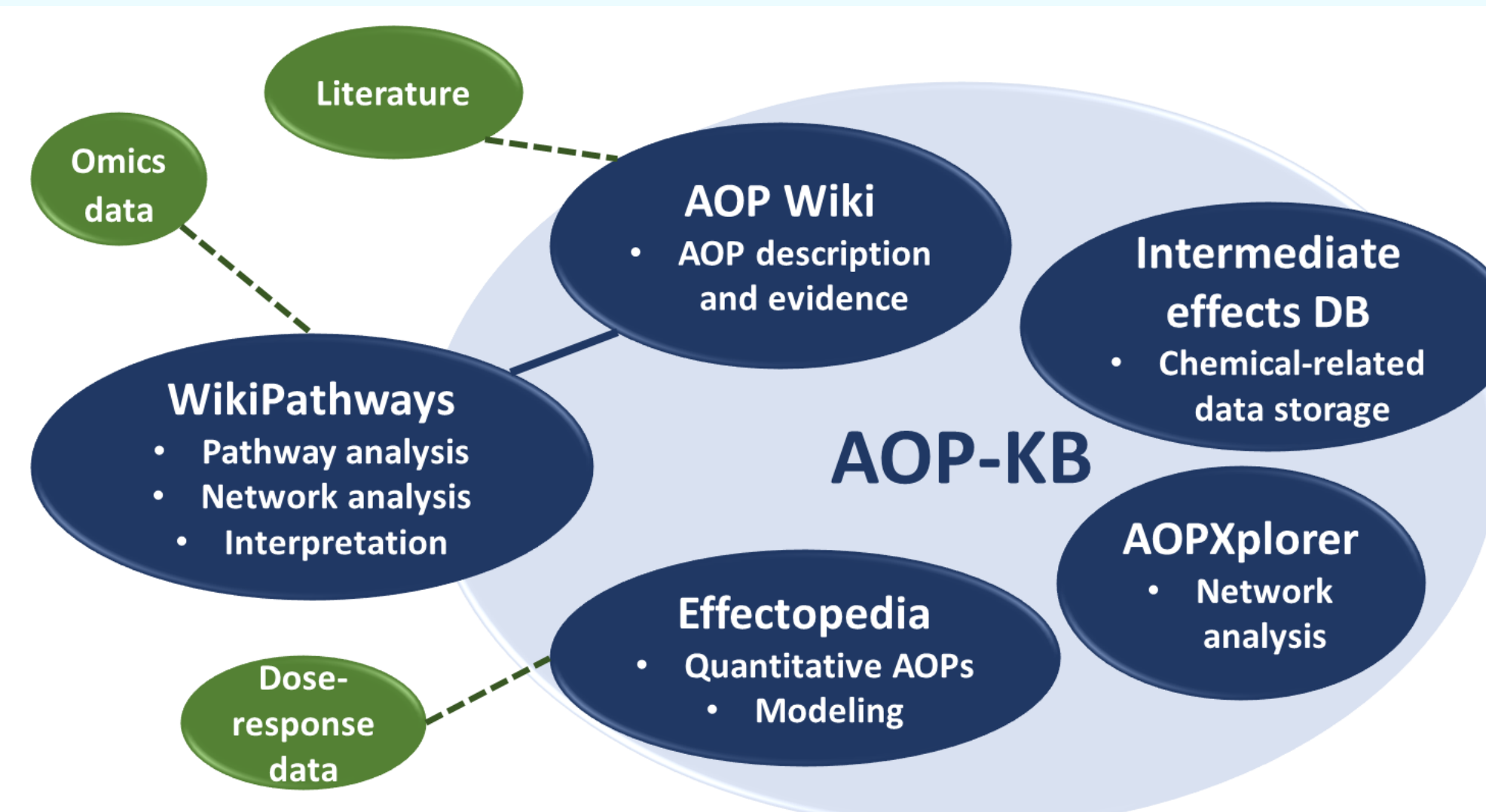


Figure 1: Illustrative description of the proposed addition to the AOP-Knowledge Base (AOP-KB).

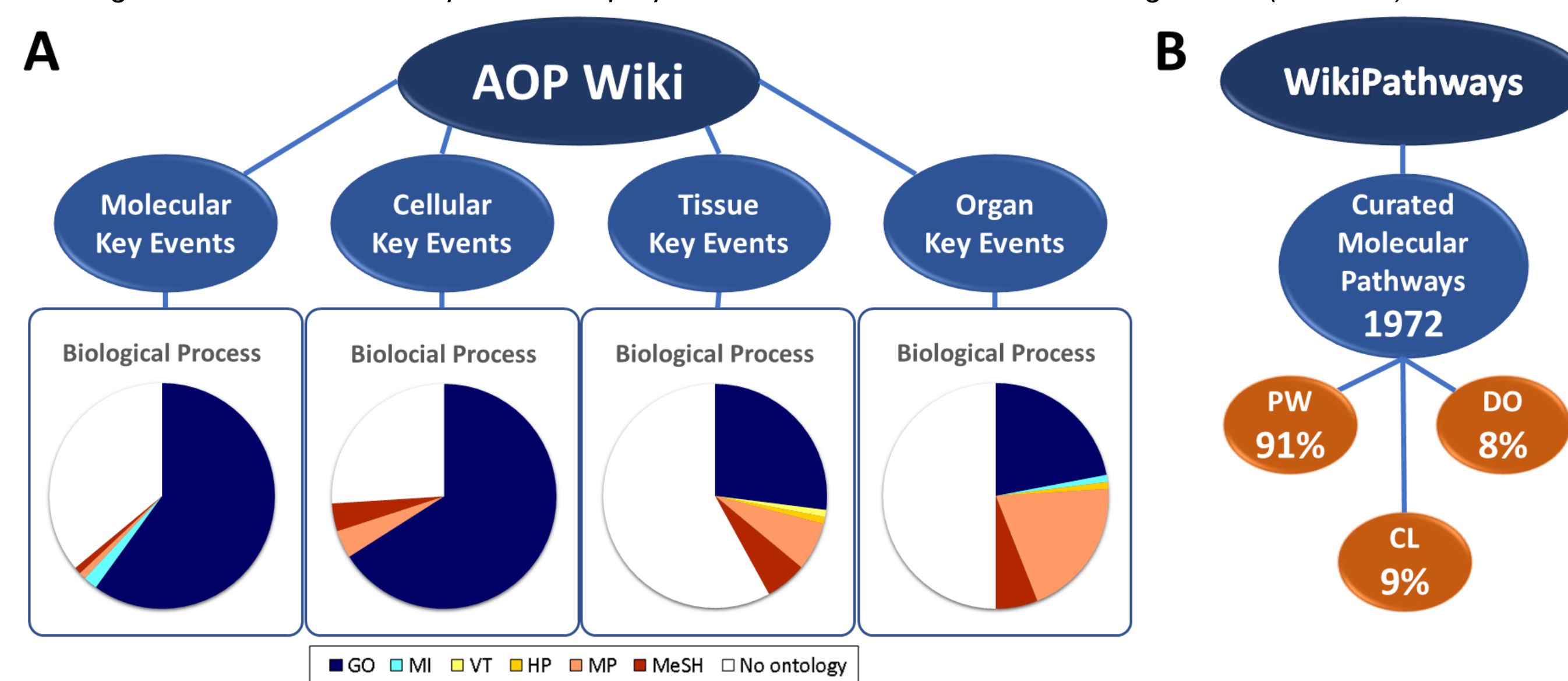


Figure 2: AOP Wiki (A) and WikiPathways (B) use a variety of ontologies which do not map directly. CHEBI: Chemical Entities of Biological Interest, CL: Cell Ontology, DO: Disease Ontology, GO: Gene Ontology, HP: Human Phenotype Ontology, MeSH: Medical Subject Headings, MI: Molecular Interactions, MP: Mammalian Phenotype Ontology, PRO: Protein Ontology, PW: Pathway Ontology, UBERON: Uber Anatomy Ontology, VT: Vertebrate Trait, WIKI: AOP Wiki.

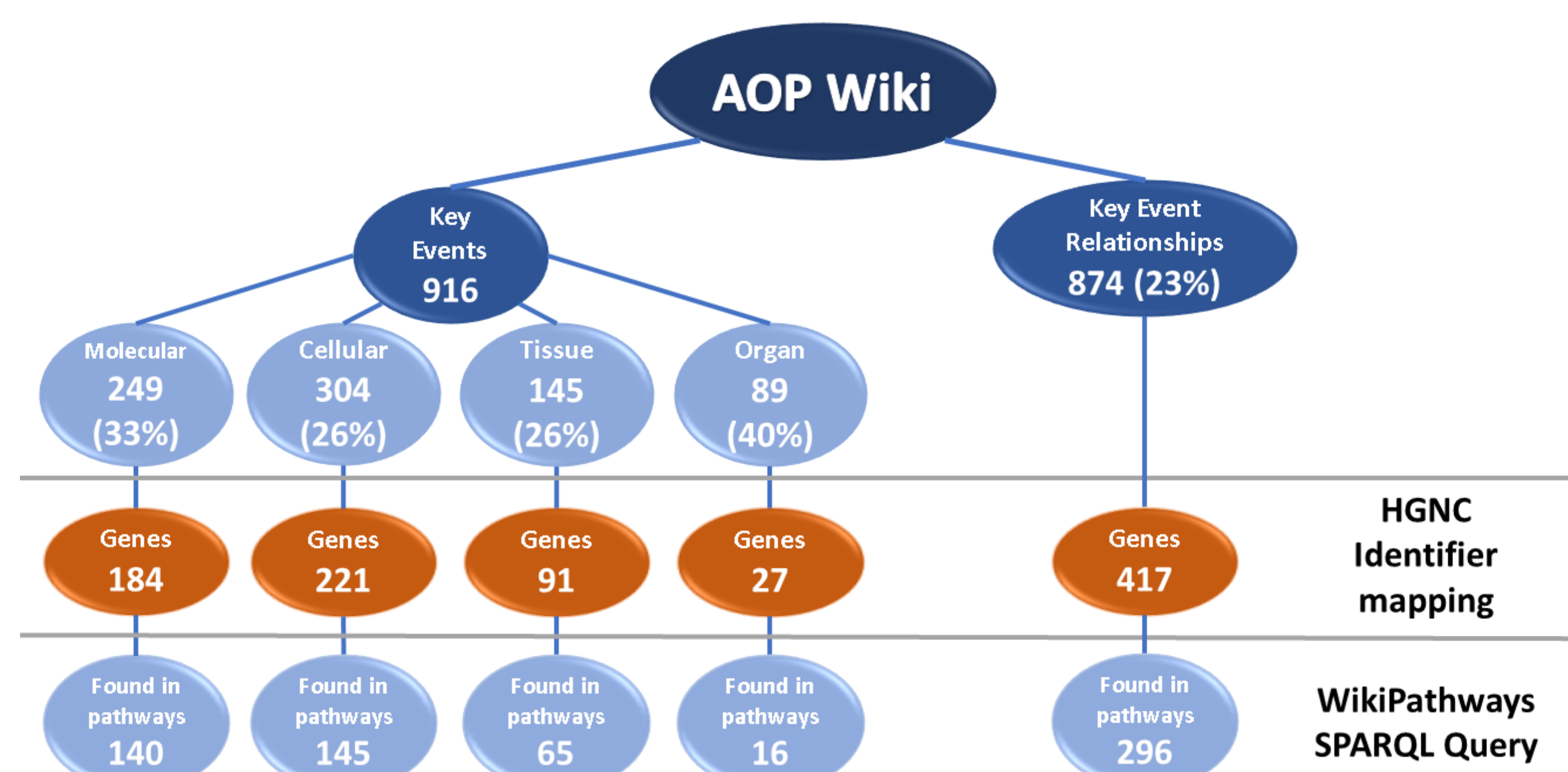


Figure 3: AOP Wiki identifier mapping highlighted genes involved in Key Events and Key Event Relationships, which were used to retrieve possible related molecular pathways in WikiPathways. Percentages indicate the relative number of descriptions completed in the AOP Wiki.

## References

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