Computationally-predicted AOPs

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How do we go from a mouse, a chip/plate, or a poke to a population... Quickly, easily, cheaply, and transparently?
**Overview of the AOP framework**

**Molecular initiating event (MIE)**
Chemical induced perturbations that affect biological systems at the molecular level.
One MIE may lead to multiple AO

**Key events (KE)**
Intermediate effects or predictive associations spanning several levels of biological association
KE are measurable

**Adverse Outcome (AO)**
This may occur at the population level for ecological outcomes or at the individual level for human health outcomes

Adapted from Noffisat Oki
AOP Discovery & Development

<100s a year

Putative AOPs

~10s a year

Formal AOPs

<10s a year

Quantitative AOPs

computationally-predicted AOPs & networks

Adapted from Steve Edwards
Data-generated connections
Inferred connections
Phenotype node
Expression node
High through put screening

DE gene expression data
Phenotype data
Other data
Enriched pathways
Discretized data
Processing
Annotated associations
HTS data

cpAOP network

Chemical

Adverse outcome

Bell et al, in submission
Direct support in cpAOP subset
Possible support in cpAOP subset
Cell cycle
DNA metabolism
Protein metabolism
Cell signaling
Extracellular matrix
Metabolic dysregulation
Lipid and metabolic dysregulation (phenotype)
Cytotoxicity inflammation
Stress response
### Adverse Outcome | Key Events
---|---
Stage 1 | Steatosis
| de novo lipogenesis
| FA oxidation
| FA uptake
| Lipid efflux

Stage 2 | Steatohepatitis
| Excess FA
| ER stress
| ROS formation
| TNFalpha activation
| Lipotoxicity
| Apoptosis

Stage 3 | Fibrosis
| Chronic inflammation
| HSC activation
| Collagen deposition

Stage 4 | Cirrhosis
| Regenerating nodules
| Angiogenesis
| Portal hypertension

Stage 5 | HCC

### Key Event with ToxCast assay
- ERBB2/4/Akt

### Key Event
- Wnt/Hedgehog signaling
- Cytotoxicity
- Apoptosis
- Cell cycle/proliferation
- Energy dysregulation
- Ketone body metabolism
- Interleukin/interferon
- Extra cellular matrix organization
- Lipid dysregulation
- Inflammation

### Phenotype
- Cancer
- Inflammation
- Steatosis

Bell et al, in submission

Angrish et al, in submission
So how do we start integrating the AOPs and cpAOPs in a computational manner?
A free and open web application where you can visualize and analyze Adverse Outcome Pathway (AOP) Networks.

[Learn more]

View an AOP
Search for an AOP and visualize it.

View an AOP Network for an Outcome
Search for all of the AOPs associated with a given outcome and view the network

Perform a Risk Screening
Use data from a number of sources to perform a quantitative risk screening for your favorite chemicals.

Related Efforts
AOPXplorer is part of the Automated Chemical Risk Screening (ACRS) System. Other related projects include:

- AOP Ontology (AOPO)
- R/Bioconductor aop package
- Bayesian Point of Departure estimates
- Natural splined-based Meta-Regression of High Throughput Screening data

AOPXplorer is also part of the Adverse Outcome Pathway Knowledgebase (AOP-KB) Universe of programs.

Slide courtesy of Lyle Burgoon
AOP Steatosis Via FXR and HSD17B4 AOP

AOP Steatosis Via IRS1, AKT2, TSC1 or TSC2 and Lipogenesis AOP

AOP Steatosis Via IRS1, AKT, GSK3 and Lipogenesis AOP

AOP Steatosis Via DHB4 AOP

Slide courtesy of Lyle Burgoon
Critical/sufficient node
AOP node

Burgoon, in submission (aop R package available on GitHub)
- Literature
- HTS
- Omics

- Evidence integration
- Leverage data mining methods

- Biological relevance
- Assay targets

- Facilitate expert curations
- Improve AOP development
Thank you

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