Using the AOP framework to aid in gene set identification

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The presenter has no conflict of interest.
The views expressed in this presentation are those of the presenter and do not necessarily reflect EPA policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.
AOPs Connect Toxicity Pathways to Regulatory Endpoints

Predictivity of measurement for AO decreases

Time between exposure and effect increases
Factors Determining Predictivity of Early Key Events

- Evidence supporting the KERs between that KE and the AO
- Quantitative understanding of the downstream KERs
- Modifying factors that influence downstream KEs & KERs
http://aopkb.org/
https://aopwiki.org/
https://www.effectopedia.org/

e.AOP.portal

Effectopedia
Detailed development of structured & computational AOPs

Intermediate Effects DB
Put chemical-related AOP components in a regulatory context

AOP-XML

AOP Wiki
Collaborative development of AOP descriptions & evidence

AOP Xplorer
Visualize attribute networks to discover & explore AOPs in a broader context

Third party
Applications, plugins
Alkylation of DNA in male pre-meiotic germ cells leading to heritable mutations

Short name: Alkylation of DNA leading to heritable mutations

Offspring: mutation in all tissues, increasing risk of disease

Relationships Among Key Events and the Adverse Outcome

<table>
<thead>
<tr>
<th>Event</th>
<th>Description</th>
<th>Triggers</th>
<th>Weight of Evidence</th>
<th>Quantitative Understanding</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA, Alkylation</td>
<td>Directly Leads to</td>
<td>Insufficient or incorrect DNA repair,</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insufficient or incorrect DNA repair, N/A</td>
<td>Directly Leads to</td>
<td>Mutations, Increase</td>
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</tbody>
</table>

Carole Yauk – https://aopwiki.org/aops/15
AOP Provides Understanding & Scaffold for Data

- Toxicity Pathways
  - Macro-Molecular Interactions
  - Cellular Responses
  - Organ Responses
  - Organism Responses
  - Population Responses
  - High Throughput Tox
  - Guideline Studies

- Regulatory Endpoints
  - Mechanistic Toxicology Data
    - Bioindicators (e.g. Molecular Epi)
  - Epidemiology
    - Eco Field Studies
AOP networks emerge as AOPs are entered into the AOP-Wiki

Key Events Shared by Multiple AOPs

AOP:30

ER Antagonism

- Hepatocyte Reduced VTG Production
- Ovary Impaired Oocyte Development
- Female Decreased Ovulation & Spawning
- Population Declining Trajectory

AOP:25

Aromatase Inhibition

- Granulosa Reduced E2 Synthesis
- Hepatocyte Reduced VTG Production
- Ovary Impaired Oocyte Development
- Female Decreased Ovulation & Spawning
- Population Declining Trajectory

AOP:23

AR Agnoism

- Hypothalamic Neurons (-) Feedback
- Theca Granulosa Reduced T & E2 Synthesis
- Hepatocyte Reduced VTG Production
- Ovary Impaired Oocyte Development
- Female Decreased Ovulation & Spawning
- Population Declining Trajectory

Linkages Shared by Multiple AOPs

Courtesy of Dan Villeneuve
AOP Title [edit]

Aromatase inhibition leading to reproductive dysfunction (in fish)
Short name: Aromatase inhibition leading to reproductive dysfunction (in fish)

Dan Villeneuve – https://aopwiki.org/aops/25
Factors Determining Predictivity of Early Key Events

- Evidence supporting the KERs between that KE and the AO
- Quantitative understanding of the downstream KERs
- Modifying factors that influence downstream KEs & KERs
Too many AOPs, too little time…
Can we automate this step?

Bell et al. (2016)
*Toxicol. Sci.*, **150**:510-520
doi:10.1093/toxsci/kfw017

Oki & Edwards (2016)
*Toxicology*, **350–352**:49–61
doi:10.1016/j.tox.2016.04.004

Oki et al. (2016)
*Current Environmental Health Reports*, **3**(1):53-63
Automating Extraction of Subnetworks

- Standardize lift values across datasets
- Community detection to approximate key events
  - Currently using random walk to identify densely connected subgraphs
- Build out from an adverse outcome or molecular initiating event of interest
cpAOP network for Fatty Liver disease from ToxCast, CTD and TG-Gates data
cpAOP generated for Fatty Liver disease by random walk community analysis

MIE/Cellular

Tissue/Organ

Adverse Outcome

Non-alcoholic Fatty Liver

Metabolic markers (glucose & cholesterol regulation), early stress response

Inflammation, cell death, pathological changes

Fatty Liver, Alcoholic

Fatty Liver

Fatty acid dysregulation & deposition

15

8

4

5

17

3

6

1

9

2

11

7

Noffisat Oki
Expert-derived Putative AOPs for Liver Steatosis

Michelle Angrish et al.  
*Toxicol. Sci.* (2016)  
150 (2): 261-268  
doi:10.1093/toxsci/kfw018
Accelerating AOP Development

Associations derived from public data sources
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- Gary Ankley
- Robert Kavlock

- Evgeniia Kazymova
- Cataia Ives
- Rose Combs
- Landon Grindheim
- Max Felsher
- Brendan Ferreri-Hanberry
- David Lyons

- Clemens Wittwehr
- Brigitte Landesmann
- Ivana Campia
- Sharon Munn
- Ahmed Sayed
- Maurice Whelan

- Hristo Aladjov
- Magda Sachana
- Joop DeKnecht

- Ed Perkins
- Lyle Burgoon
- Natalia Garcia Reyero

- Collaborative Partners
  - OECD External Advisory Group on Molecular Screening & Toxicogenomics
  - IPCS/WHO Mode of Action Steering Committee
Chemical Safety for Sustainability cpAOP Team

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- Maureen Pittman

- CTD Team
  - Carolyn Mattingly
  - Benjamin King
  - Allan Peter Davis
- NIEHS Collaborator
  - Scott Auerbach
- Mixtures Collaborator
  - Jane Ellen Simmons

- cpAOP Collaborators
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  - Charles Wood
  - Brian Chorley
  - Dan Villeneuve
  - Sean Watford
  - Keith Houck

- ADME/AEP Collaborators
  - Cecilia Tan
  - Jeremy Leonard
Questions?

SYSTEMS TOXICOLOGY