What is an AOP (and What ISN'T It?)

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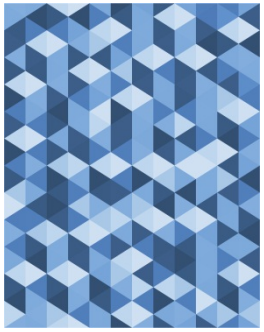
Adverse Outcome Pathways: From Research to Regulation

September 3-5, 2014

Views expressed in this presentation are those of the presenter and not necessarily those of the U.S. Food and Drug Administration

Outline

- Define AOP

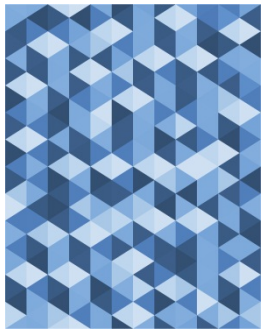


- Define Goals and Set Reasonable Expectations

- Lessons Learned from Surrogate Biomarkers

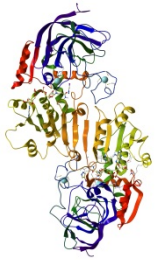
- Challenges in Adoption of New Approaches

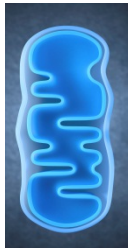
What is an AOP?

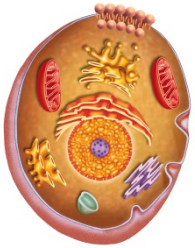


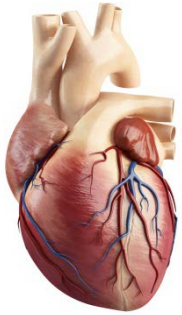
- Pathway:
  - Molecular initiating event
  - Intervening steps – all known (but may involve other pathways)
  - Adverse phenotypic change *in vivo*
- Think in terms of linearity but each key event within an AOP can be influenced by other pathways
- Envision network of interacting processes
- "An AOP differs from the NRC's "toxicity pathway" concept…which is primarily cell-based.. The AOP explicitly includes the progression of events from the molecule to the population level"

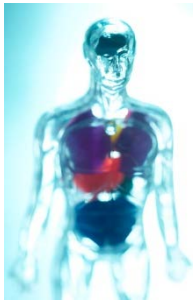
Integrating Emerging Technologies into Chemical Safety Assessment, The Expert Panel on the Integrated Testing of Pesticides, Council of Canadian Academies, http://www.scienceadvice.ca/en/assessments/completed/pesticides.aspx; User's Handbook Supplement to the Guidance Document for Developing and Assessing AOPS





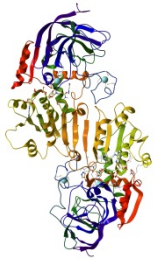
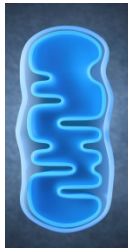
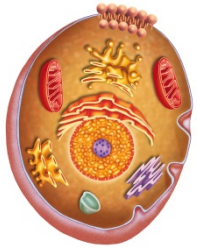
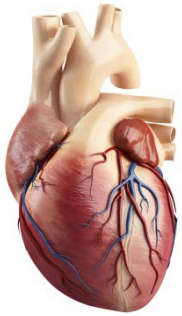
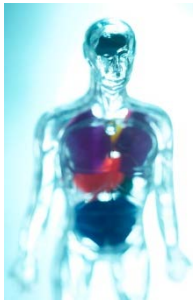






Exposure	Molecular Interaction	Organelle Effect	Cellular Effect	Organ Effect	Individual Effect	Population Effect

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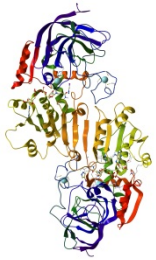
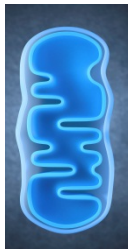
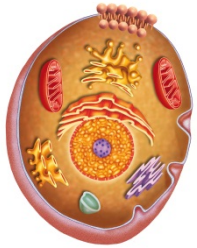
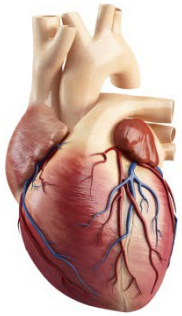
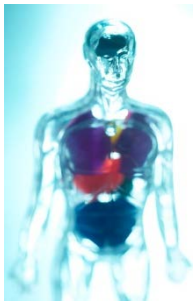
How to get there:
Genomics, proteomics, metabolomics, high content screening, computational modeling,
Integration of these data with classical endpoints!











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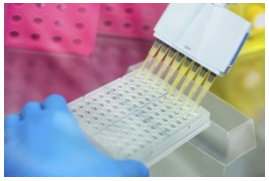
Future?



What Isn't an AOP?

- Mechanism of toxicity: initiating event to possible cellular effect
  - e.g., mitochondrial toxicity

- Mode of action: correlate initiating toxicant to adverse event without biological context
  - e.g., trichloroethylene causes congenital heart defects

Integrating Emerging Technologies into Chemical Safety Assessment, The Expert Panel on the Integrated Testing of Pesticides, Council of Canadian Academies, http://www.scienceadvice.ca/en/assessments/completed/pesticides.aspx; http://www.epa.gov/ttn/atw/hlthef/tri-ethy.html; Tom Knudsen, personal communication

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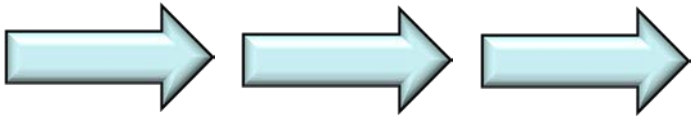
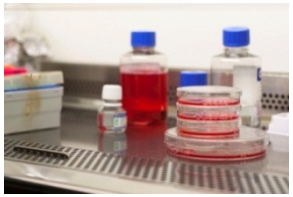
- Lessons Learned from Surrogate Biomarkers
- Challenges in Adoption of New Approaches

Assay Type

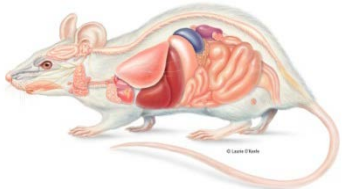
Screening  Replacement

Define Goals

- Compound screening followed by classical testing



- Regulatory animal tests
  - Improve accuracy or replace



- Human responses
  - Inform population-based or individual responses?

Carefully Define Expectations

- Examples of past over-promising
  - Monoclonal antibodies will be magic bullet to cure cancer
  - Toxicogenomics will replace animal testing
- State expected accuracy, timeframe and caveats
- Are the new approaches correlated to *in vivo* animal results, human exposures, etc.?

Challenges

- A complete understanding of molecular mechanisms of drugs and chemicals is rare and insufficient to predict damage to organs
  - Acetaminophen (APAP) responsible for >50% of acute liver injury in the US. Most studied drug in the world yet still learning more about its mechanism
  - Drugs “toxic to mitochondria” have diverse phenotypic outcomes
  - Susceptibility to damage and its outcome may be due to innate immunity differences between individuals
- “DILI is multi-factorial, potentially involving the adaptive immune system, infections, environment (age, diet) and genetics”
- Many drugs induce toxicity via metabolites and ability to predict metabolites is still poor (computational modeling) and most *in vitro* cells lack DMEs

Tujios and Fontana, Nat. Rev. Gastroenterol. Hepatol. 8, 202–211, 2011;
Han et al., Trends Pharmacol Sci 34:243-253, 2013

Promise

- "The multidisciplinary Systems Toxicology approach combines principles of chemistry, computer science, engineering, mathematics, and physics with high content experimental data obtained at the molecular, cellular, organ, organism, and population levels to characterize and evaluate interactions between potential hazards and the components of a biological system"

- Will add to knowledge base in how changes to homeostatic systems leads to adverse events

- This will empower the development and use of AOPs and lead to improvement in safety assessment and human medicine

Sturla et al. Chem. Res. Toxicol. 27: 314−329, 2014

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Surrogate Endpoints

- Clinical endpoint: A characteristic or variable that reflects how a patient feels, functions, or survives

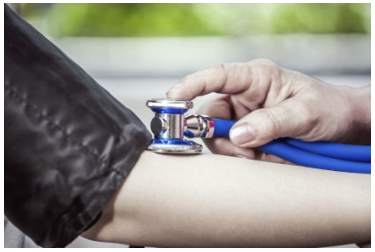
- Surrogate endpoint: A biomarker that is intended to substitute for a clinical endpoint
  - Patients may not feel benefit of biomarker changes

- Must have evidence it is in casual pathway, has history of intervention with a drug

Temple JAMA. 282:790-795, 1999; Desai and Temple AAPS J. 8:E146-152, 2006

Reduction of Elevated Blood Pressure

- Was strongly argued to be adaptive and protective
- Epidemiology shows correlation between elevated blood pressure and strokes and coronary heart disease
- Demonstrated in many clinical trials



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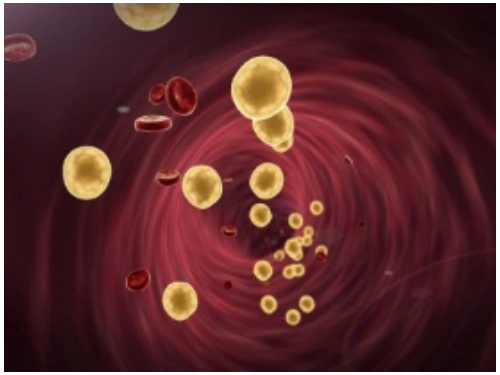
Effects on Blood Lipid Levels

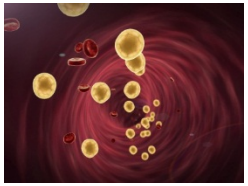
- Pathogenesis is well-studied

- Agents that lower LDL and/or raise HDL assumed to reduce risk of cardiovascular disease



Ezetimide

- Lowers LDL and approved by the FDA



- ENHANCE trial: Ezetimide + simvastatin found further elevations of LDL but no difference in cardiac intima media thickness was observed. Latter is measure of atherosclerosis and should be closer to the disease endpoint than lipids

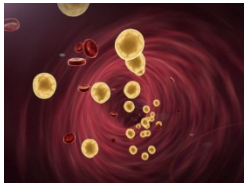
- Remains commonly used in US (although did decline after ENHANCE trial) and use increased in Canada

- “The drug continues to defy gravity…”

Psaty and Lumley JAMA 299:1474-1476, 2008; Lu et al. Am Heart J. 167:683-689, 2014; Mitka JAMA 311:1279-1280, 2014

Cholesteryl Ester Transfer Protein (CETP) Inhibitors

- Torcetrapib
  - Elevated HDL but no effect on progression of coronary atherosclerosis; treated patient group had more major cardiovascular events and mortality



- Dalcetrapib
  - Elevated HDL but had no effect on short-term and long-term cardiovascular events

- Manufacturers stopped development but two more drugs in this class are in clinical trials

Psaty and Lumley JAMA 299:1474-1476, 2008; Wright Curr Opin Cardiol. 28:389-398, 2013

Lessons Learned

- Drugs targeting what was thought to be well-studied biological events leading to morbidity and mortality

- Illustrates our lack of biological understanding and serves as a cautionary tale

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If You Build It, They May Not Come

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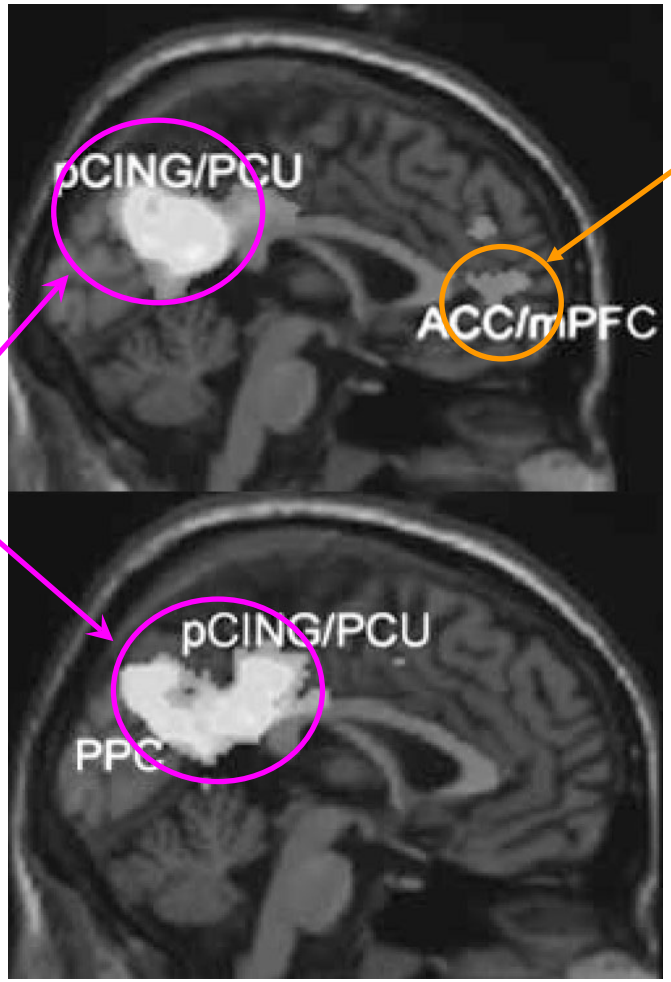
- Motivated reasoning
  - Prior belief effect
    - Pay more attention to information that reflects baseline belief
  - Confirmation bias
    - Seek out information that confirms prior belief
  - Disconfirmation bias
    - Spend more time reading contrary arguments to counter their conclusions

Strickland et al., J Health Polit Policy Law 36:935-944, 2011

Biological Evidence



Emotions concerning contradiction to own belief

General emotion processing

Slide courtesy of Dr. Serguei Liachencko, FDA/NCTR; Westen et al., J Cogn Neurosci. 18:1947-1958, 2006

Conclusion from fMRI Study

- "As predicted, motivated reasoning was not associated with neural activity in regions previously linked to cold reasoning tasks and conscious (explicit) emotion regulation."

Westen et al., J Cogn Neurosci 18:1947-1958, 2006

Roadblocks

- Depends on how new assays will be used
  - Replacements for regulatory acceptance need to meet very high bars
- As seen with Ezetimide, some clinicians are not practicing evidence-based medicine
  - Need to find way to get sponsors, regulators, etc. comfortable with new approaches

Solution?

- Learn that the generation and dissemination of evidence alone are insufficient

- Show how the new information will fit their beliefs/concerns vs. being threatening
  - e.g., if replacement assay, how can a sponsor identify whether something is a false positive?

Kahan et al., J Risk Res 14: 147-174, 2011; http://culturalcognition.squarespace.com/

Roadblocks

- To reach the broadest market, sponsor will need to meet regulatory guidelines in all countries of interest

- Therefore, just getting replacement assays accepted in one country, may not stop a sponsor from performing the original tests

Light at the End of the Tunnel

- Current methods are expensive, time-consuming, use many animals and lack required accuracy so much room for improvement
- Ability to improve screening for further testing is first hurdle
- Replacement of current regulatory assays will take more data and time but can happen

Acknowledgements

- NCTR
  - William Mattes (Division of Systems Biology)

- EPA
  - Thomas Knudsen (National Center for Computational Toxicology)