Linkage of Exposure and Effects using Genomics, Proteomics, and Metabolomics in Small Fish Models

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Science Question

- How can we improve extrapolation across life stages/endpoints (biological levels of organization), species (including under-represented taxa) and from the lab to field for single chemicals and complex mixtures?
- Can we establish functional linkages between changes at the molecular level and phenotypic outcomes relevant for risk assessment for multi-organ biological systems well conserved among vertebrates?
- Can we develop integrated, biologically-based computational models that use mechanism of action as a basis for predicting adverse outcomes?

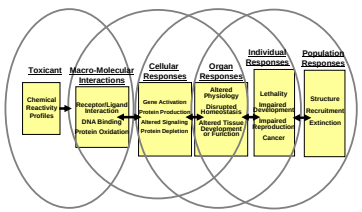
Research Goals

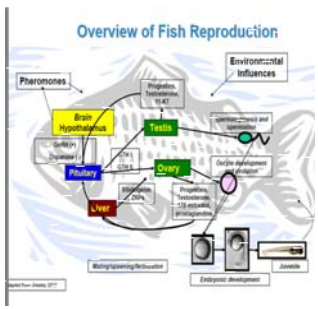
- Identify novel molecular markers of effects of exposure to chemicals representing different mechanisms of action (MOA) within the vertebrate hypothalamic-pituitary-gonadal (HPG) axis
- Link these biomarkers to responses relevant to ecological risk assessment
- Support development of integrated modeling approaches that utilize MOA as a basis for prediction of adverse outcomes

Specific Approach

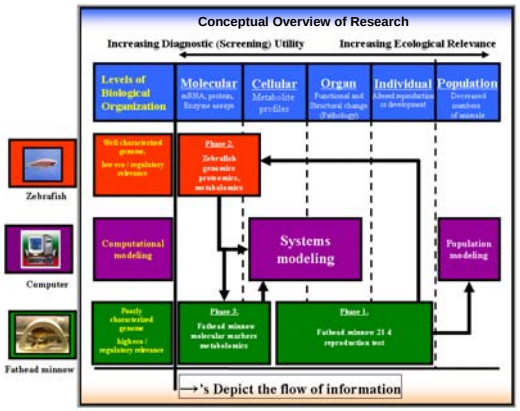
1. Investigate effects of chemical probes on the HPG axis using definitive tests in the fathead minnow to establish initial toxicity pathways and ecologically- relevant responses (Phase 1)
2. Identify transcriptomic , proteomic, metabolomic, and other whole-animal responses to the same chemicals using short-term zebrafish exposures (Phase 2)
3. Validate genomic markers in the fathead minnow with an emphasis on time-course of responses and/or compensation and recovery after exposure (Phase 3)
4. Concurrently integrate data from above in a systems modeling context, as well as relevant population modeling

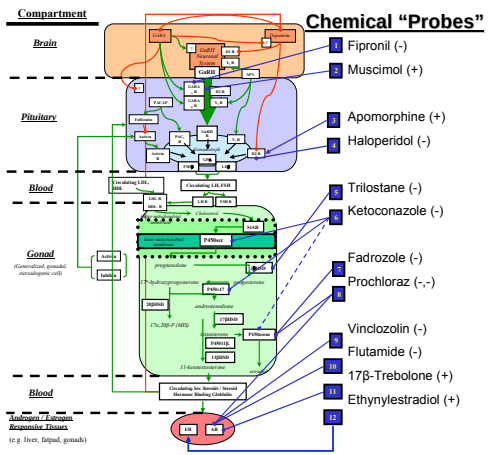
Defining Toxicity/Adverse Outcome Pathways





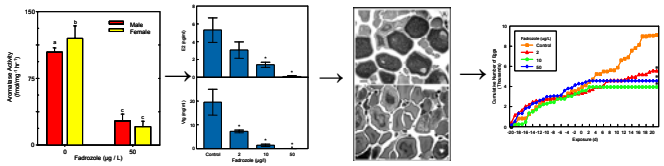
Methods/Approach



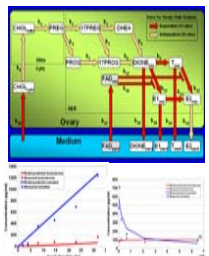


Results/Conclusions

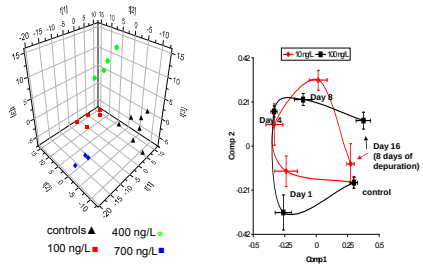
Definition of Novel Toxicity/Adverse Outcome Pathways (Ankley et al. 2009)



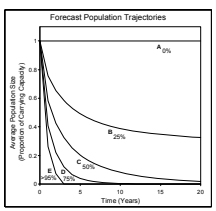
Computational Model of Vertebrate Steroidogenesis (Breen et al. 2007)



Metabolomics for Defining Pathways and Exposure Reconstruction (Ekman et al. 2008; 2009)



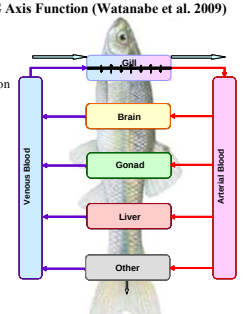
Translating Biochemical Alterations into Population-Level Responses (Miller et al. 2007)



Impact and Outcomes

Physiologically-Based Model for Predicting Estrogen Effects on HPG Axis Function (Watanabe et al. 2009)

Gill: Chemical Uptake
Brain: Signaling
Gonad: Steroid Production
Liver VTG Production
Other: Elimination
Blood: Transport



Determining the Extent of the Impact