Print

Hahn Lab at WHOI: Research Interests

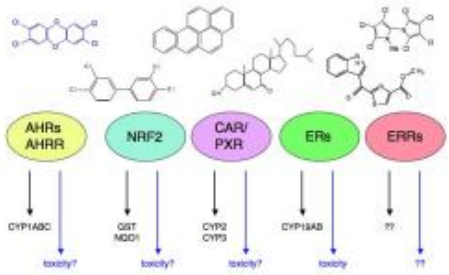
The overall objective of research in our laboratory is to understand the biochemical and molecular mechanisms that underlie the interactions of animals with their chemical environment. We examine these mechanisms from comparative and evolutionary perspectives in order to understand the fundamental features of the biochemical systems that control the response of animals to toxic chemicals. Our research is guided by general questions such as:

• How did chemical signaling pathways evolve in metazoans?

• What is the role of these pathways in adaptation to long-term chemical exposure?

• What is the mechanistic basis for differential sensitivity to chemicals among species and populations of animals?

• What are the mechanisms by which chemicals disrupt embryonic development?



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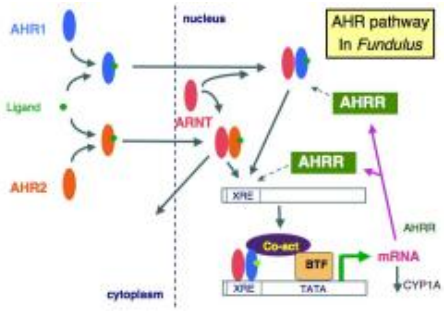
Xenobiotic Receptors



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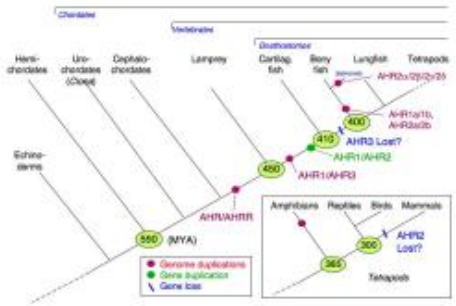
AHR pathway in killifish (*Fundulus heteroclitus*)

Additional Information:

Our current research projects are described under the Research Projects tab (choose at left). The following text (below) provides some additional background and describes some of our research findings obtained over the past several years, with a listing of representative publications that provide additional details.

Much of our research has focused on the halogenated aromatic hydrocarbons (HAHs), a group of chemicals that includes the chlorinated dibenzo-*p*-dioxins, polychlorinated biphenyls (PCBs), halogenated diphenyl ethers, as well as a variety of marine natural products. Some of these compounds are highly toxic, especially to vertebrate animals. Some of the most toxic HAHs cause toxicity by binding to and activating the aryl hydrocarbon receptor (Ah receptor or AHR).

The AHR is a ligand-activated transcription factor and the first protein in a signal transduction pathway that c ulminates in the altered expression of genes involved in the control of cell growth and differentiation. The AHR works in concert with a related protein, the aryl hydrocarbon receptor nuclear translocator (ARNT). Both the AHR and ARNT are members of the bHLH-PAS family of transcriptional regulatory proteins. The AHR controls both adaptive and toxic responses to planar aromatic compounds, including planar HAHs (PHAHs) such as the chlorinated dioxins and some PCBs, as well as polynuclear aromatic hydrocarbons (PAHs). Our research on the AHR and PAS family combines comparative and evolutionary approaches with the application of molecular methods to understand the unity and diversity of these signaling pathways. Through this basic research in cell and molecular biology, using environmental contaminants and marine natural products as molecular probes, we hope to contribute to an understanding of the mechanisms by which aquatic animals respond to chemical contaminants and the evolutionary history of the proteins involved. Through this research we also seek to use aquatic animal models to provide insight into human health consequences of exposure to environmental chemicals.



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Evolutionary History of AHR genes

Models for AHR Research

	Biomedical models	Evolutionary models	Environmental targets & models
Mammals	human, mouse	opossum, platypus	whales, seals, mink, polar bear
Birds	chicken	chicken	terns, albatross, cormorant
Amphibians/ Reptiles	*Xenopus* spp. (frog)	*Xenopus* spp., *Chrysemys*	*Chrysemys* (turtle)
Bony fishes	zebrafish, medaka	Takifugu (Fugu), Tetraodon	killifish (*Fundulus*), rainbow trout, Atlantic salmon
Cartilaginous fishes		spiny dogfish	dogfish, skate, sharks
Jawless fishes		lamprey, hagfish	
Invertebrates (Deuterostomes)	Amphioxus, *Strongylocentrotus* (sea urchin)	Ciona, Amphioxus, *Strongylocentrotus*	
Invertebrates (Protostomes)	*Drosophila*, *C. elegans*	*Drosophila*, *C. elegans*	*Mya*, *Mytilus*, *Dreissena*
Invertebrates (Basal metazoans)		*Nematostella*, *Trichoplax*	

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Models for AHR Research

Here are brief summaries of some of the research we have conducted:

Phylogenetic diversity and molecular evolution of the AHR and the PAS gene family.

To explore the diversity and comparative biochemistry of AHRs, we have sequenced multiple AHR cDNAs from over two dozen aquatic species, including birds, marine mammals, fishes, an amphibian, a tunicate, an echinoderm, and mollusks. We have compared the structures and functions of these and other AHRs. These studies have revealed a greater diversity of AHR genes in fishes as compared to mammals. Initially this involved the identification of the second AHR form (AHR2) in fishes and birds, while more recently we have found evidence of additional AHR gene diversity in bony and cartilaginous fishes. For example, in some species of bony fishes, duplications at the AHR1 and AHR2 loci have produced four (and sometimes more) distinct AHR genes in a single fish species (e.g. pufferfish *Takifugu rubripes*). These studies also have shown that invertebrate AHRs are unable to bind the typical ligands of vertebrate AHRs, such as TCDD and beta-naphthoflavone (BNF). These studies have been summarized in a series of papers and reviews:

Hahn, M. E., and Karchner, S. I. (2011). Chapter 27. Structural and Functional Diversification of AHRs during Metazoan Evolution. In *The Ah receptor in Biology and Toxicology* (R. Pohjanvirta, Ed.). John Wiley & Sons, Inc. (in press)

Hahn, M. E., Karchner, S. I., Evans, B. R., Franks, D. G., Merson, R. R., and Lapseritis, J. M. (2006). Unexpected diversity of aryl hydrocarbon receptors in non-mammalian vertebrates: Insights from comparative genomics. Journal of Experimental Zoology 305(9):693-706. Review.

Hahn, M.E. (2002) Aryl hydrocarbon receptors: Diversity and Evolution. Chem.-Biol. Interact. 141: 131-160.

Hahn, M. E., Merson, R. R., and Karchner, S. I. (2005). Xenobiotic Receptors in Fishes: Structural and Functional Diversity and Evolutionary Insights. In Biochemistry and Molecular Biology of Fishes. Vol. 6 - Environmental Toxicology (T. W. Moon, and T. P. Mommsen, Eds.), pp. 191-228.

Hahn, M.E. (1998) The Aryl Hydrocarbon Receptor: A Comparative Perspective. Comp. Biochem. Physiol. 121C(3):23-53.

Hahn, M.E., Karchner, S.I., Shapiro, M.A., and Perera, S.A. (1997) Molecular evolution of two vertebrate aryl hydrocarbon (dioxin) receptors (AHR1 and AHR2) and the PAS family. Proc. Natl. Acad. Sci. U.S.A. 94: 13743-13748 .

AHR Signaling in Mammalian and Nonmammalian Models.

We have utilized several vertebrate model systems (fish, mammalian cell lines) to investigate the function of the AHR signaling pathway and its role in normal developmental processes and in the developmental toxicity of chlorinated dioxins and related chemicals. The studies take advantage of the fact that fish possess AHR and AHRR paralogs that are co-orthologs of the mammalian AHR and AHRR genes. Some recent papers include:

Merson, R. R., Karchner, S. I., and Hahn, M. E. (2009). Interaction of fish aryl hydrocarbon receptor paralogs (AHR1 and AHR2) with the retinoblastoma protein. *Aquat Toxicol* 94, 47-55.

Merson, R. R., Hersey, S. P., Zalobowski, T. W., Albanese, A. R., Franks, D. G., and Hahn, M. E. (2009). Aryl hydrocarbon Receptors (AHR) of sharks: Structural and functional divergence among AHR paralogs. *Toxicological Sciences (The Toxicologist Supplement)* 108, 15 (Abstract #81).

Karchner, S. I., Jenny, M. J., Tarrant, A. M., Evans, B. R., Kang, H. J., Bae, I., Sherr, D. H., and Hahn, M. E. (2009). The active form of human aryl hydrocarbon receptor repressor lacks exon 8 and its Pro185 and Ala185 variants repress both AHR and HIF. *Molecular and Cellular Biology* 29, 3465-3477.

Jönsson, M. E., Franks, D. G., Woodin, B. R., Jenny, M. J., Garrick, R. A., Behrendt, L., Hahn, M. E., and Stegeman, J. J. (2009). The tryptophan photoproduct 6-formylindolo[3,2-b]carbazole (FICZ) binds multiple AHRs and induces multiple CYP1 genes via AHR2 in zebrafish. *Chemico-biological interactions* 181, 447-454.

Jenny, M. J., Karchner, S. I., Franks, D. G., Woodin, B. R., Stegeman, J. J., and Hahn, M. E. (2009). Distinct roles of two zebrafish AHR repressors (AHRRa and AHRRb) in embryonic development and regulating the response to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Toxicol Sci* 110, 426-441.

Hahn, M. E., Allan, L. L., and Sherr, D. H. (2009). Regulation of Constitutive and Inducible AHR Signaling: Complex Interactions Involving the AHR Repressor. *Biochemical Pharmacology* 77, 485-497.

Evans, B. R., Karchner, S. I., Allan, L. L., Pollenz, R. S., Tanguay, R. L., Jenny, M. J., Sherr, D. H., and Hahn, M. E. (2008). Repression of aryl hydrocarbon receptor (AHR) signaling by AHR repressor: role of DNA binding and competition for AHR nuclear translocator. *Mol Pharmacol* 73, 387-398.

Evans, B. R., Karchner, S. I., Franks, D. G., and Hahn, M. E. (2005). Duplicate aryl hydrocarbon receptor repressor genes (ahrr1 and ahrr2) in the zebrafish Danio rerio: Structure, function, evolution, and AHR-dependent regulation in vivo. *Arch. Biochem. Biophys.* 441, 151-167.

Karchner, S. I., Franks, D. G., and Hahn, M. E. (2005). AHR1B, a new functional aryl hydrocarbon receptor in zebrafish: tandem arrangement of ahr1b and ahr2 genes. *Biochem. J.*, 392: 153-161.

Karchner, S. I., and Hahn, M. E. (2004). Pufferfish (Fugu rubripes) aryl hydrocarbon receptors: unusually high diversity in a compact genome. *Mar. Environ. Res.* 58, 139-140 (abstract).

Yang, X., Liu, D., Murray, T. J., Mitchell, G. C., Hestermann, E. V., Karchner, S. I., Merson, R. R., Hahn, M. E., and Sherr, D. H. (2005). The Aryl Hydrocarbon Receptor Constitutively Represses c-myc Transcription in Human Mammary Tumor Cells. *Oncogene* 24: 7869–7881.

Karchner, S.I., Franks, D.G., Powell, W.H., and Hahn, M.E. (2002) Regulatory Interactions Among Three Members of the Vertebrate Aryl Hydrocarbon Receptor Family: AHR Repressor, AHR1, and AHR2. *J. Biol. Chem.* 277: 6949-6959.

Karchner, S.I., Powell, W.H., and Hahn, M.E. (1999) Structural and Functional Characterization of Two Highly Divergent Aryl Hydrocarbon Receptors in the teleost Fundulus heteroclitus. Evidence for a novel class of ligand-binding bHLH-PAS factors. *Journal of Biological Chemistry* 274: 33814-33824 .

Mechanisms and Consequences of Evolved PCB/Dioxin Resistance in Fish.

Research in our lab has explored the evolution of PCB/dioxin resistance in the Atlantic killifish (*Fundulus heteroclitus*) following long-term exposure of fish to dioxins and PCBs at Superfund sites. As part of the Superfund Basic Research Program at Boston University, we are investigating the role of AHRs in the mechanism of this evolved resistance. We identified polymorphic alleles at the AHR1, AHR2, and AHR Repressor (AHRR) loci in fish from New Bedford Harbor, MA (PCB-resistant) and Scorton Creek, MA (PCB-sensitive). All three loci are highly polymorphic and the distribution of SNPs and non-synonymous SNPs and inferred haplotypes (specific arrangements of SNPs on a single chromosome) varies among sites. A substantial fraction of the inferred haplotypes for each gene are site specific. Some AHR1 and AHR2 haplotypes are more frequently observed in fish from contaminated sites, whereas other haplotypes are under-represented in these fish. These results provide the first large-scale characterization of AHR gene family variability among sites and identifies specific AHR1 and AHR2 haplotypes as candidate resistance alleles in relation to the mechanism of evolved PCB/dioxin resistance in killifish.

We also are collaborating with Dr. Isaac Wirgin at New York University to understand the mechanism of resistance to PCBs in Atlantic tomcod (*Microgadus tomcod*) inhabiting the Hudson River. Those studies have revealed that Hudson River tomcod possess AHR2 variants with impaired ability to bind TCDD:

> Wirgin, I., Roy, N. K., Loftus, M., Chambers, R. C., Franks, D. G., and Hahn, M. E. (2011). Mechanistic Basis of Resistance to PCBs in Atlantic Tomcod from the Hudson River. *Science* 331, 1322-1325 (Published Online 1317 February 2011, DOI: 1310.1126/science.1197296). WHOI Press release. Science article.

Oleksiak, M. F., Karchner, S. I., Jenny, M. J., Franks, D. G., Mark Welch, D. B., and Hahn, M. E. (2011). Transcriptomic assessment of resistance to effects of an aryl hydrocarbon receptor (AHR) agonist in embryos of Atlantic Killifish (*Fundulus heteroclitus*) from a Marine Superfund Site. *BMC Genomics*, 12, 263.

Aluru, N., Karchner, S. I., and Hahn, M. E. (2011). Role of DNA methylation of AHR1 and AHR2 promoters in differential sensitivity to PCBs in Atlantic Killifish, *Fundulus heteroclitus*. *Aquat Toxicol* 101, 288-294.

Greytak, S. R., Tarrant, A. M., Nacci, D., Hahn, M. E., and Callard, G. V. (2010). Estrogen responses in killifish (*Fundulus heteroclitus*) from polluted and unpolluted environments are site- and gene-specific. *Aquat Toxicol* 99, 291-299.

Merson, R. R., Karchner, S. I., and Hahn, M. E. (2009). Interaction of fish aryl hydrocarbon receptor paralogs (AHR1 and AHR2) with the retinoblastoma protein. *Aquat Toxicol* 94, 47-55.

Matson, C. W., Clark, B. W., Jenny, M. J., Fleming, C. R., Hahn, M. E., and Di Giulio, R. T. (2008). Development of the morpholino gene knockdown technique in Fundulus heteroclitus: a tool for studying molecular mechanisms in an established environmental model. *Aquat Toxicol* 87, 289-295.

Burnett, K. G., Bain, L. J., Baldwin, W. S., Callard, G. V., Cohen, S., Di Giulio, R. T., Evans, D. H., Gómez-Chiarri, M., Hahn, M. E., Hoover, C. A., Karchner, S. I., Katoh, F., MacLatchy, D. L., Marshall, W. S., Meyer, J. N., Nacci, D. E., Oleksiak, M. F., Rees, B. B., Singer, T. P., Stegeman, J. J., Towle, D. W., Veld, P. A. V., Vogelbein, W. K., Whitehead, A., Winn, R. N., and Crawford, D. L. (2007). Fundulus as the premier teleost model in environmental biology: Opportunities for new insights using genomics. *Comparative Biochemistry and Physiology* D2, 257-286.

Tarrant, A. M., Greytak, S. R., Callard, G. V., and Hahn, M. E. (2006). Estrogen receptor-related receptors in the killifish Fundulus heteroclitus: diversity, expression, and estrogen responsiveness. *J. Mol. Endocrinol.* 37, 105-120.

Merson, R. R., Franks, D. G., Karchner, S. I., and Hahn, M. E. (2006). Development and characterization of polyclonal antibodies against the aryl hydrocarbon receptor protein family (AHR1, AHR2, and AHR repressor) of Atlantic killifish Fundulus heteroclitus. *Comp Biochem Physiol C Toxicol Pharmacol* 142, 85-94.

Hahn, M.E., Karchner, S.I., Franks, D.G., and Merson, R.R. (2004) Aryl hydrocarbon receptor polymorphisms and dioxin resistance in Atlantic killifish (Fundulus heteroclitus). *Pharmacogenetics* 14:131-146.

Powell, W.H., H.G. Morrison, E.J. Weil, S.I. Karchner, M.L. Sogin, J.J. Stegeman, and M.E. Hahn. (2004) Cloning and analysis of the CYP1A promoter from the Atlantic killifish (Fundulus heteroclitus). *Marine Environmental Research* 58: 119-124.

Meyer, J.N., Wassenberg, D.M., Karchner, S.I., Hahn, M.E., and DiGiulio, R.T. (2003) Expression and inducibility of aryl hydrocarbon receptor (AHR) pathway genes in wild-caught killifish (Fundulus heteroclitus) with different contaminant exposure histories. *Environ. Toxicol. Chem.* 22: 2337-2343.

Bello, S.M., Franks, D.G., Stegeman, J.J., and Hahn, M.E. (2001) Acquired Resistance to Aryl Hydrocarbon Receptor Agonists in a Population of Fundulus heteroclitus from a Marine Superfund site: In Vivo and In Vitro Studies on the Induction of Xenobiotic Metabolizing Enzymes. *Toxicol. Sci.* 60: 77-91.

The AHR as a Chemical Susceptibility Gene.

We have characterized AHRs in marine mammals, birds, and fish and investigated their possible roles in controlling species differences in sensitivity to HAH toxicity. This research has shown that many marine mammals, including cetaceans (whales) and pinnipeds (seals), possess high-affinity forms of AHR. The presence of such AHRs suggests that these species are sensitive to HAHs in their environment. In contrast, some species of birds possess AHRs with reduced affinity for TCDD and also display reduced sensitivity to TCDD, PCBs, and other HAHs. We have traced these differences to two positions in the ligand-binding domain; the identity of amino acids at these positions predicts the species sensitivity to HAHs—an example of a molecular biomarker of susceptibility.

Farmahin, R., Manning, G., Crump, D., Wu, D., Mundy, L., Jones, S., Hahn, M. E., Karchner, S., Giesy, J., Bursian, S., Zwiernik, M. J., Fredricks, T., and Kennedy, S. (2012). Amino Acid Sequence of the Ligand Binding Domain of the Aryl Hydrocarbon Receptor 1 (AHR1) Predicts Sensitivity of Wild Birds to Effects of Dioxin-like Compounds.
Toxicol Sci. (in press)

Farmahin, R., Wu, D., Crump, D., Herve, J. C., Jones, S. P., Hahn, M. E., Karchner, S. I., Giesy, J. P., Bursian, S. J., Zwiernik, M. J., and Kennedy, S. W. (2012). Sequence and In Vitro Function of Chicken, Ring-Necked Pheasant, and Japanese Quail AHR1 Predict In Vivo Sensitivity to Dioxins.
Environmental Science & Technology 46, 2967-2975.

Jensen, B. A., Reddy, C. M., Nelson, R. K., and Hahn, M. E. (2010). Developing tools for risk assessment in protected species: Relative potencies inferred from competitive binding of halogenated aromatic hydrocarbons to aryl hydrocarbon receptors from beluga (*Delphinapterus leucas*) and mouse. *Aquat Toxicol* 100, 238–245.

Farmahin, R., Wu, D., Bursian, S. J., Crump, D., Giesy, J. P., Hahn, M. E., Jones, S. P., Karchner, S. I., Mundy, L. J., Zwiernik, M. J., and Kennedy, S. W. (2010). The ligand binding domain—The key to the classification of avian sensitivity to dioxin-like compounds.*Toxicology letters* 196S, S116-117 (P108-010).

Head, J. A., Hahn, M. E., and Kennedy, S. W. (2008). Key amino acids in the aryl hydrocarbon receptor predict dioxin sensitivity in avian species. *Environmental Science & Technology* 42, 7535-7541.

Yasui, T., Kim, E. Y., Iwata, H., Franks, D. G., Karchner, S. I., Hahn, M. E., and Tanabe, S. (2007). Functional characterization and evolutionary history of two aryl hydrocarbon receptor isoforms (AhR1 and AhR2) from avian species. *Toxicol Sci* 99, 101-117.

Karchner, S. I., Franks, D. G., Kennedy, S. W., and Hahn, M. E. (2006). The molecular basis for differential dioxin sensitivity in birds: Role of the aryl hydrocarbon receptor. *Proc. Natl. Acad. Sci. U.S.A.* 103, 6252-6257.

Kim, E.-Y., and Hahn, M. E. (2002). cDNA cloning and characterization of an aryl hydrocarbon receptor from the harbor seal (Phoca vitulina): A biomarker of dioxin susceptibility? *Aquat. Toxicol.* 58, 57-73.

Jensen, B. A., and Hahn, M. E. (2001). cDNA cloning and characterization of a high affinity aryl hydrocarbon receptor in a cetacean, the beluga, Delphinapterus leucas. *Toxicol. Sci.* 64, 41-56.

Karchner, S. I., Kennedy, S. W., Trudeau, S., and Hahn, M. E. (2000). Towards a molecular understanding of species differences in dioxin sensitivity: Initial characterization of Ah receptor cDNAs in birds and an amphibian. *Mar. Environ. Res.* 50, 51-56.

Natural Products as Ligands for the AHR and other Xenobiotic Receptors

The AHR was originally discovered because of its role in mediating effects of synthetic HAHs. However, receptors and enzymes that appear to function primarily in adaptive responses to xenobiotic chemicals often have endogenous ligands and substrates as well. Similarly, receptors for well-known hormones and growth factors often are targets of natural products.

We have been involved in a series of collaborative studies to understand the chemical specificity of vertebrate and invertebrate AHRs. These studies have identified a number of marine natural products, including some persistent brominated and chlorinated aromatics, that can activate the AHR. In addition, natural indoles isolated from mammalian tissues can act as AHR agonists and natural flavonoids can

act as antagonists.

Jönsson, M. E., Franks, D. G., Woodin, B. R., Jenny, M. J., Garrick, R. A., Behrendt, L., Hahn, M. E., and Stegeman, J. J. (2009). The tryptophan photoproduct 6-formylindolo[3,2-b]carbazole (FICZ) binds multiple AHRs and induces multiple CYP1 genes via AHR2 in zebrafish. *Chemico-Biological Interactions* 181, 447-454.

Reddy, C. M., Stegeman, J. J., and Hahn, M. E. (2008). Chapter 7: Organic Pollutants: Presence and Effects in Humans and Marine Animals. In *Oceans and Human Health: Risks and Remedies from the Seas* (P. J. Walsh, S. L. Smith, Lora E. Fleming, H. M. Solo-Gabriele, and W. H. Gerwick, Eds.), pp. 121-144. Academic Press / Elsevier, Burlington, MA.

Vetter, W., Hahn, M. E., Tomy, G., Ruppe, S., Vatter, S., Chahbane, N., Lenoir, D., Schramm, K.-W., and Scherer, G. (2005). Biological activity and physico-chemical parameters of the marine halogenated natural products 2,3,3´,4,4´,5,5´-heptachloro-2´-methyl-1,2´-bipyrrole (Q1) and 2,4,6-tribromoanisole (TBA). Arch. *Environ. Contam. Toxicol.* 48, 1-9.

Tittlemier, S.A., Kennedy, S.W., Hahn, M.E., Reddy, C.M., and Norstrom, R.J. (2003) Naturally-produced halogenated dimethyl bipyrroles bind to the Ah receptor and induce cytochrome P4501A and porphyrin accumulation in chicken embryo hepatocytes. *Environ. Toxicol. Chem.* 22: 1497-1506.

Song, J., Clagett-Dame, M., Peterson, R.E., Hahn, M.E., Westler, W.M., Sicinski, R.R., and DeLuca, H.F. (2002) A Novel Ligand for the Aryl Hydrocarbon Receptor Isolated from Lung. *Proc. Natl. Acad. Sci. U.S.A.* 99: 14694-14699.

Billiard, S.M., Hahn, M.E., Franks, D.G., Peterson, R.E., Bols, N.C., and Hodson, P.V. (2002) Binding of polycyclic aromatic hydrocarbons (PAHs) to teleost aryl hydrocarbon receptors (AHRs). *Comparative Biochemistry and Physiology B* 133: 55-68.

We also have investigated the role of natural products as feeding deterrents and the adaptations of predators that allow them to consume chemically defended marine organisms through the expression and induction of xenobiotic-metabolizing enzymes.

Whalen, K. E., Starczak, V. R., Nelson, D. R., Goldstone, J. V., and Hahn, M. E. (2010). Cytochrome P450 diversity and induction by gorgonian allelochemicals in the marine gastropod *Cyphoma gibbosum*. *BMC Ecology* 2010, 10:24 (doi:10.1186/1472-6785-10-24).

Whalen, K. E., Sotka, E. E., Goldstone, J. V., and Hahn, M. E. (2010). The role of multixenobiotic transporters in predatory marine molluscs as counter-defense mechanisms against dietary allelochemicals. *Comp Biochem Physiol C Toxicol Pharmacol* 152, 288-300.

Whalen, K. E., Lane, A. L., Kubanek, J., and Hahn, M. E. (2010). Biochemical warfare on the reef: the role of glutathione S-transferases in consumer tolerance of dietary prostaglandins. *PLoS ONE* 5, e8537 (http://dx.plos.org/8510.1371/journal.pone.0008537).

Mechanisms of Response to Oxidative Stress

During embryonic and fetal development, animals are especially sensitive to chemicals causing oxidative stress. The developmental expression and inducibility of anti-oxidant defenses is a critical factor affecting susceptibility to oxidants at these early life stages. In mammalian systems, oxidant and pro-oxidant chemicals elicit an anti-oxidant response, referred to as the "oxidative stress response (OSR)", which involves the increased expression of genes whose products act to mitigate the oxidant challenge. We have initiated studies to establish zebrafish as a model for studying mechanisms of developmental toxicity and the role of oxidative stress.

Timme-Laragy, A. R., Karchner, S. I., Franks, D. G., Jenny, M. J., Harbeitner, R. C., Goldstone, J. V., McArthur, A. G., and Hahn, M. E. (2012). Nrf2b: a novel zebrafish paralog of the oxidant-responsive transcription factor NF-E2-related factor 2 (Nrf2). *J. Biol. Chem. 287:* 4609-4627.

Timme-Laragy, A. R., Karchner, S. I., and Hahn, M. E. (2010). Gene knockdown by morpholino-modified oligonucleotides in the zebrafish model: applications for developmental toxicology. In *Methods in Molecular Biology: Developmental Toxicology* (J. M. Hansen, and C. Harris, Eds.). Humana Press.

Hahn, M. E., Karchner, S. I., Franks, D. G., Woodin, B. R., Barott, K. L., Cipriano, M. J., and McArthur, A. G. (2008). The transcriptional response to oxidative stress in fish embryos and cells exposed to tert-butylhydroquinone (tBHQ) or 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). *Mar Environ Res* 66, 138.

Hahn, M. E., Karchner, S. I., Franks, D. G., Woodin, B. R., Barott, K. L., Cipriano, M. J., and McArthur, A. G. (2007). The transcriptional response to oxidative stress in zebrafish embryos. *Toxicological Sciences (The Toxicologist Supplement)* 96, 326-327 (Abstract #1578).

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