

## Introduction

*Michael K. Stoskopf*

"It's no fish ye're buying, it's men's lives"  
(Sir Walter Scott 1816).

"When you were a tadpole and I was fish  
In the Paleozoic time. . ."  
(Langdon Smith 1895).

Why study fish? Perhaps Langdon Smith expressed a more enlightened view of the relationships between man and teleosts than that held by many modern day researchers. The continuity of biological diversity is the key to wise use of comparative medical investigation; and the words of Sir Walter Scott, although out of context, certainly express the stakes involved with an appropriate nod to the role of economics in the process.

Nearly two decades ago, I had the opportunity to write an invited review paper on aquatic models of human disease for *ILAR News* (Stoskopf 1983). It was an interesting project, and it garnered considerable positive comment from colleagues around the world. At that time, not unlike now, various political, economic, and scientific pressures were demanding more efficient and less expensive whole animal toxicology screening methods as well as ways to reduce the use of mammals in research. At the same time, the jeopardy of our aquatic resources was becoming obvious to the general public. Looking back at that review, I am excited to see the advances that dedicated researchers have made in the sophistication and diversity of fish models for human health research in the intervening time. It is also encouraging to see the levels of National Institutes of Health funding being provided to researchers working with zebrafish (*Danio rerio*), the current popular candidate for fish-mouse substitute. The zebrafish does indeed provide an excellent tool for investigations into developmental and several genetic questions. It would have been relatively simple to fill this issue with papers on zebrafish models alone. However, the zebrafish cannot be all things to all models. Other fish models are receiving far less attention and funding support than they

deserve. Therefore, in planning the issue, I have tried to achieve balance and emphasize the value of the diversity of good fish models in biomedical research.

Obviously, a single issue of one journal cannot do justice to the value of fish models in modern medical science. However, the authors, the Editorial Board, and I hope that the issue will provide thoughtful readers with insight into the diversity and complexity of fish and the potential this diversity offers for challenging research and monitoring problems. A previous issue of *ILAR Journal* titled "Fish, Amphibians, and Reptiles" (ILAR 1995) focused on guidelines for the appropriate care and management of these species in laboratories (Detolla et al. 1995). The articles in that issue provided an important update and review of the guidelines for care and use of fish in research, including a summary of appropriate anesthesia, analgesia, and euthanasia techniques. Readers can find more information on husbandry and disease management of fish in dedicated chapters in new editions of textbooks in laboratory animal medicine, which are now appropriately seeking to address those questions for laboratory fishes (Fox et al. 2001; Ostrander 2001). Certainly, fish as research animals do present some important challenges for laboratory animal veterinarians and institutional animal care and use committees. There remains a major need for more information based on good investigative research into the biology and husbandry of laboratory fishes.

However, this issue seeks to take the reader a step farther and, in the tradition of the journal for mammalian models, present the scientific details of some of the more important uses of laboratory fish in biomedical research. Dr. Mac Law (2001) provides us with a pathologist's view of fish models and their usefulness in disease research. His contribution, titled "Mechanistic Considerations in Small Fish Carcinogenicity Testing," introduces the reader to the regulatory pressures that have pushed the need for less expensive and quicker bioassays than the standard 2-yr rodent protocols before presenting a review of the advantages and challenges of different exposure designs and delivery routes when using fish for carcinogenicity testing. This review forms a useful background for his discussion of DNA adduct research in the study of mutagenesis as a mechanism of carcinogenesis, with particular attention to the value of immunohistochemistry studies in small fish. His call for more knock-out and transgenic fish tools for mechanistic research in carcinogenesis should be heeded.

Many of the models described in this issue argue the similarity of the systems or mechanisms being studied to

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those in humans. This is only one valuable approach to comparative medical research. Dr. Renate Reimschuessel (2001) introduces us to the value of investigating differences in analogous adaptations in fish and furthermore describes how the diversity of fishes provides the necessary tools for the creative research scientist to investigate aspects of physiology that cannot be isolated in mammalian models. Renal disease is a common primary and secondary health problem affecting millions of people of all ages. In her article "A Fish Model of Renal Regeneration and Development," Dr. Reimschuessel describes how the ordinary goldfish, along with zebrafish, tilapia, toadfishes, and several other fish species, may help lead us to a new understanding of the mechanisms of renal repair through research into nephron neogenesis. Excellent concise reviews of vertebrate renal development, the special anatomy and diversity of the teleost kidney, and renal repair in mammals and fish give the reader the necessary background to appreciate the value of the fish models of nephron neogenesis in the quest to identify ways to stimulate de novo nephrogenesis in diseased mammalian kidneys. Perhaps even more important, the models Dr. Reimschuessel presents provide a template for how scientists searching for ways to gain insight into complex molecular and physiological questions in other areas of human health research can find valuable ways to work around mammalian model limitations by using fish models.

In "Development of Sensory Systems in Zebrafish (*Danio rerio*)," Dr. Stephen Moorman (2001) provides the reader with powerful arguments for the extensive use of these small fish for studies of developmental and genetic analysis. This one fish species has received considerable attention by the National Institutes of Health, which also strongly supports the zebrafish genome initiative. Although development of sensory systems is only one area where the zebrafish is providing valuable insight into human clinical disorders, it is a very exciting area of breakthrough research. Dr. Moorman's article provides the reader with a brief overview of each specific sensory system in the adult zebrafish, followed by a more detailed description of how each of the sensory systems develops, before he discusses the mutant strains of zebrafish with specific developmental defects in that sensory system. Readers can find even more information about zebrafish mutants by visiting <<http://zfin.org>> and other useful zebrafish websites that can be reached by links from the ILAR web site (<<http://www.national-academies.org/ilar>>).

Although zebrafish are currently commanding most of the attention and funding opportunities in fish models of human disease, they are relative newcomers in this area of research. Inbred genetic strains of live-bearing platyfish and swordtails (genus *Xiphophorus*) have been available and in use in comparative oncology models since the early 1930s. In the mid-1960s, long before the isolation of the *Xmrk* gene or the *CDKN2X* gene, *Xiphophorus* models were being used to hypothesize their existence. In their article titled "*Xiphophorus* Interspecies Hybrids as Genetic Models of Induced Neoplasia," Drs. Ron Walter and Steven Kazianis (2001) carefully set the historical stage and introduce the

reader to the *Xiphophorus* Genetic Stock Center (<[www.xiphophorus.org](http://www.xiphophorus.org)>), which maintains more than 60 pedigreed lines representing most species of the genus. They then provide us with an extensive review of the Gordon-Kosswig melanoma model with detailed discussions of the *Xmrk-1* and *Xmrk-2* oncogene, and the *Diff* tumor suppressor in the fish model. Mouse model enthusiasts who work in oncogenesis should not miss this review. Drs. Walter and Kazianis proceed to discuss the inducible *Xiphophorus* tumor models in detail, including the controversial UV-induced melanoma models, chemical carcinogen-induced models, and the use of these models for studying DNA repair potential. As a finale, they provoke the reader to consider the value of spontaneous melanoma models and other models associated with aging in *Xiphophorus*, which have not been used extensively to date.

Dr. Richard Winn's (2001) article "Transgenic Fish as Models in Environmental Toxicology" provides the reader with a useful overview of several applications of transgenic fish models in environmental toxicology studies. He provides us with a well-balanced account of the state of transgenic fish model development and relates it to the achievements with which readers may be more familiar in development of transgenic rodent models. His discussion of transgenic medaka, with multiple copies of bacteriophage LIZ vector with the *lacI* and *cII* bacterial genes as mutational targets, helps remind us how mechanistically similar the fish model is to the most widely used transgenic rodent mutation assay. Dr. Winn points out some of the great challenges facing transgenic fish as models of human disease. One of these problems is the challenge of sustaining gene expression in transgenic fish lineages, a challenge rooted in the common use of mosaic integration of transgenes in founder fish into fin and other superficial tissues. What is the problem? Fish developed in this way often do not transmit the transgene or transmit it at very low frequencies.

Dr. Winn also addresses the major issue preventing transgenic fish models from reaching their true potential in the investigation of human disease. He strongly supports integration of laboratory fish husbandry and facilities into traditional laboratory animal management paradigms and points out that transgenic fish model development cannot approach its potential as long as researchers themselves are the primary care providers for their fish. He advocates increased standards, practices, and facilities for the care and use of fish, consistent with those for mammals, and increased training of laboratory animal caretakers in the care and use of fish in general and transgenic fish in particular. This message bears the close attention of *ILAR Journal* readers.

It is my sincere hope that this will be only the first of many issues of *ILAR Journal* that address nonmammalian models in biomedical research. I am very thankful to the editors for their professional and meticulous approach to the challenge of assembling this issue. Their help and guidance was invaluable. I am particularly grateful to the authors who took valuable time from their research to share their very specialized knowledge and to provide us with the important,

up-to-date information that is found in this issue of fascinating and informative papers.

“Fish, flesh, or fowl, commend all summer long,  
whatever is begotten, born and dies.  
Caught in that sensual music all neglect, monuments  
of unaging intellect”

(William Butler Yeats 1928).

## References

- Detolla LJ, Srinivas S, Whitaker BR, Andrews C, Hecker B, Kane AS, Reimschuessel R. 1995. Guidelines for the care and use of fish in research. *ILAR J* 37:159-173.
- Fox JG, Anderson LC, Loew FM, Quimby FW, eds. 2001. *Laboratory Animal Medicine*, 2nd ed. San Diego: Academic Press.
- ILAR [Institute of Laboratory Animal Resources]. 1995. Fish, amphibians, and reptiles. *ILAR J* 37:158-202.
- Law JM. 2001. Mechanistic considerations in small fish carcinogenicity testing. *ILAR J* 42:274-284.
- Moorman SJ. 2001. Development of sensory systems in zebrafish (*Danio rerio*). *ILAR J* 42:292-298.
- Ostrander GK, ed. 2001. *The Handbook of Experimental Animals: The Laboratory Fish*. London: Academic Press.
- Reimschuessel R. 2001. A fish model of renal regeneration and development. *ILAR J* 42:285-291, 305-308.
- Scott W. 1816. *The Antiquary*. In: Hewitt D, ed. 1996. *Books by Walter Scott*. New York: Columbia University Press.
- Smith L. 1895. *Evolution*. [HtmlResAnchor http://www.net2business.com/koontz/evolve.html](http://www.net2business.com/koontz/evolve.html).
- Stoskopf MK. 1983. Aquatic animals as models in biomedical research. *ILAR News* 26:22-27.
- Walter RB, Kazianis S. 2001. *Xiphophorus* interspecies hybrids as genetic models of induced neoplasia. *ILAR J* 42:299-304, 309-321.
- Winn RN. 2001. Transgenic fish as models in environmental toxicology. *ILAR J* 42:322-329.
- Yeats WB. 1957. *Sailing to Byzantium*. In: Allt P, Alspack RK, eds. *The Variorum Edition of the Poems of W. B. Yeats*. New York: Macmillan. p 407-408.