Zebrafish: A model for heart development

Adult zebrafish

More than just pets

Covered with iridescent scales and black stripes, zebrafish (*Danio rerio*) are popular in home aquariums. However, these little one- to two-inch fish, natives of India's Ganges River, are also helping biomedical researchers learn about how our hearts develop and function—and what can make them fail.

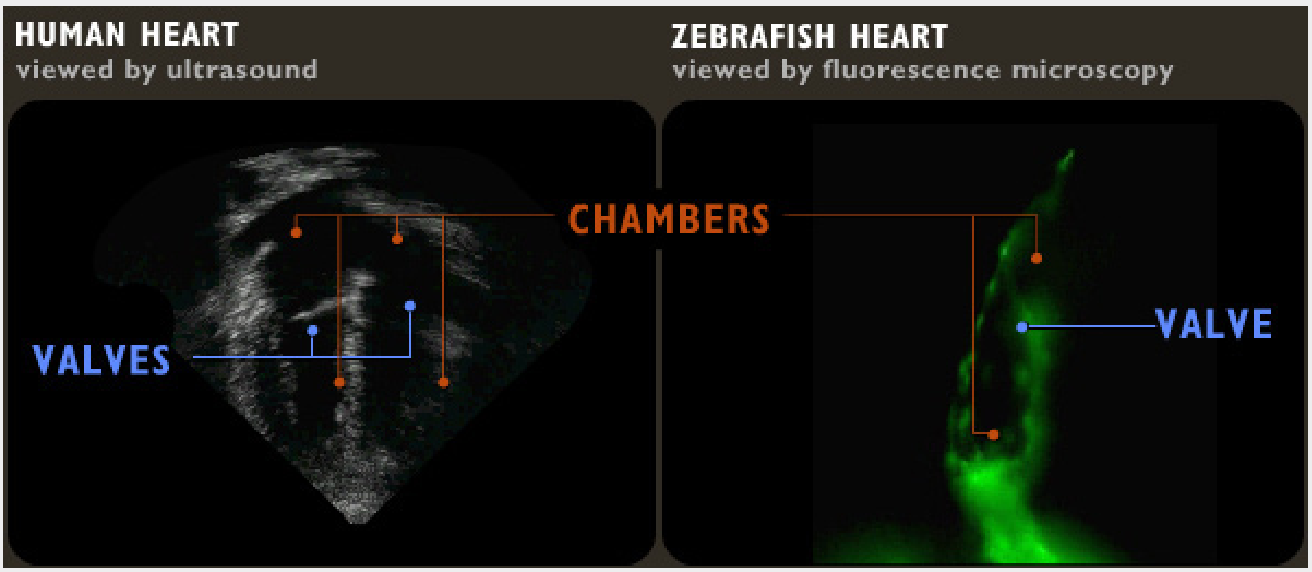
Why look at a fish?

Since the 1990s, zebrafish have proven to be a powerful tool in trying to understand how the human body develops. In addition, its genome is being sequenced (and should be complete by the end of 2008), making this model organism even more useful. Adults are relatively easy to keep in the lab, they grow up and reproduce in about three months, and, perhaps most importantly, they are vertebrates that lay small eggs (about 1 millimeter across) with clear shells that develop rapidly into translucent embryos. By peering at these embryos through a microscope, researchers can watch for abnormal development of vital organs such as the heart.

Developing zebrafish embryo

Zebrafish embryos are particularly well-suited to investigating the mysteries of heart disorders, because even embryos that develop severely malformed, nonbeating hearts can survive and continue to grow for several days. Because of the embryo's small size, it does not need a working heart. As it turns out, the cells of this model organism do not depend on the circulation of blood for oxygen during its first few days of development: They can survive with the oxygen that diffuses in from the watery surroundings for the first week of life. Luckily, this is long enough for researchers to make crucial observations about how these defective hearts form and malfunction over time.

How is your heart like that of a zebrafish?
Though distantly related, human and zebrafish hearts have much in common. Both are muscles designed to pump oxygen-carrying blood through the body. In both cases, the heart is made up of chambers with valves that ensure blood flows in the correct direction. And, in both cases, the heart pumps in a regular, rhythmic, way. The rhythmic beating of the heart in part depends on specialized heart muscle cells called *myocytes* that are normally a highly organized part of the heart's structure.



Human and zebrafish hearts

Can a zebrafish help solve medical mysteries?
Because zebrafish hearts are so similar to our own, scientists are using the fish to study many aspects of heart disease, particularly the role of genetic mutations that might cause heart abnormalities.

One disease, called *familial hypertrophic cardiomyopathy* (HCM), is the leading cause of sudden death in young athletes. Researchers discovered that mutations in a gene that codes for a heart protein called *troponin T* are responsible for 15% of the cases of HCM. But until recently, how the mutation might cause the disease remained a mystery.

Scientists had been studying a collection of zebrafish mutants that developed heart abnormalities. The most severe of this collection was a defect named *silent heart*; embryos with this mutation had hearts that did not beat at all. Using molecular techniques, researchers found the gene that, when mutated, produces silent heart also encodes the zebrafish version of the troponin T protein. In the case of silent heart, they found the gene so mutated that it failed to make any useful troponin T, and that this affected the production of two other important heart proteins. The failure of this system of proteins created disorganized heart muscle cells (myocytes) that in turn failed to organize into a heart effective at circulating blood. In humans with HCM, myocytes are also disorganized, which can lead to an abnormal heartbeat, and in some cases, sudden death.

By examining the effects of the silent heart mutation in zebrafish, more light can be shed on how mutations in the human troponin T could result in HCM in humans. Researchers hope to find still more parallels between zebrafish heart mutants and heart disease in humans. Understanding the genetics and biology behind heart formation and function will help scientists design therapies and interventions in the future to help keep hearts healthy.