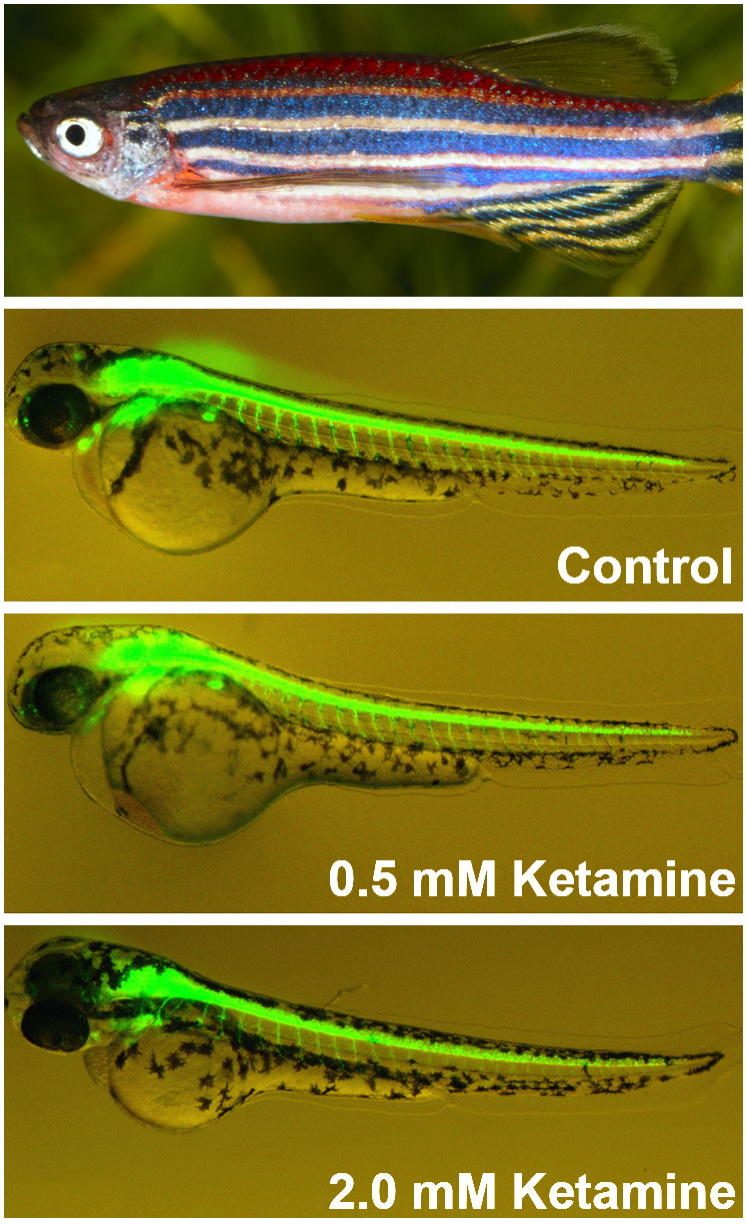
Zebrafish Make a Splash in FDA Research



Zebrafish, like humans, have a backbone and many genes in common with humans. In one laboratory test, the addition of the chemical ketamine—a pediatric anesthetic—lowers the fish's heart rate and reduces the number of neurons (nerve cells), shown in the slide as short, vertical lines coming down from the horizontal spinal cord.

A tiny fish no wider than your thumbnail may someday make a big difference to your health, but not because it's going to show up on your dinner plate.

Zebrafish—so named for the speckled "stripes" along its side and originally found in the Ganges River in East India and Burma—have been making a splash in the world of scientific research for some time. In 2003, the National Institutes of Health (NIH) ranked the torpedo-shaped fish the third most important experimental organism after rats and mice, and it's quickly gaining ground.

At the Food and Drug Administration's (FDA) National Center for Toxicological Research (NCTR) in Arkansas, scientists are using the embryos and larvae (up to five- to six-days old) of these transparent fish to practice what is called "predictive toxicology."

According to FDA research biologist Jyotshna Kanungo, Ph.D., "Using the embryos of zebrafish as models, we study how various drugs and chemicals affect the organs and systems. We try to get the best possible picture of the hazard that would be involved in taking a drug before it is tested in human patients."

In 2009, Kanungo set up the zebrafish laboratory at NCTR. "Zebrafish make terrific preclinical trial subjects, she says. "They are similar to humans in many ways and have a number of advantages over the other animals used in experimental research, such as laboratory mice and rats, because of their fast development and low cost of maintenance."

A Lot Like Us

What makes this little fish such a great scientific subject?

Surrounded by 288 fish tanks in her lab at NCTR, Kanungo notes that unlike the fruit flies and the nematode worm, other popular species studied in laboratories, zebrafish are vertebrates

"If we expose zebrafish to a drug or chemical and we observe adverse effects, that serves as a red flag and alerts us to take a closer look for toxicity."

(have a backbone), as are humans. Most of their genes—more than 80 percent—have a human counterpart, she says.

"Because the fish share so many common biological pathways with humans, they make excellent test subjects," says Merle Paule, Ph.D., director of NCTR's Division of Neurotoxicology. (Biological pathways, a series of actions among molecules in a cell, are important to how a body functions.)

The similarities don't stop there. The hearts of zebrafish and humans both have chambers and rhythmically pump oxygen-carrying blood through the body. The eyes of a zebrafish have a retinal structure much like those in people. The tiny fish also have a liver, pancreas, kidneys and intestines.

And you can see right through them.

"It's very exciting, because under a microscope you can watch as their organs and systems develop," Kanungo says. "You can actually see the blood flowing and the heart beating."

Their embryos and eggs –which are fertilized externally and develop outside of the mother's body—are available year-round. "We can watch as the cells of the embryo divide and form different parts of the larvae's body," Kanungo notes. In the span of only two to four days, cells make the eyes, the heart, the liver, the stomach and other functional organs.

Plus, the fish are small, no longer than two or three centimeters, and lay their eggs in large quantities. "In our lab at NCTR, we have the capacity to house about 6,000 of them," Kanungo notes. Introducing drugs or chemicals to the fish is just a matter of putting these compounds into the water. The fish absorb them through their skin.

In the Lab: NCTR Studies

Being able to maintain so many fish at one time also helps NCTR researchers rapidly conduct large numbers of chemical, genetic or pharmaceutical tests. "We can test 20 different concentrations of a drug or chemical in just ten minutes," Kanungo notes, and screen as many as 384 embryos within the same time period.

Today, NCTR is using the zebrafish in a number of different studies.

- Scientists are studying the effects of ketamine (a pediatric anesthetic regulated by FDA) on the overall development of embryos as well as on the cardiovascular and nervous systems.
- Using genetically-altered zebrafish embryos, scientists are investigating the effect of copper nanoparticles—frequently used in medical devices, paints and fabrics—on biological systems.
- Zebrafish have neuromasts (small sensory patches) similar to those lining the inner ear of humans. Using dyes, scientists can stain the neuromasts to make them more visible and monitor the effects of compounds such as nicotine, ketamine, and ethanol on hearing.
- Using zebrafish, scientists have shown that both ketamine and nicotine act as endocrine disruptors that interfere with normal hormonal levels.

Paule explains that while zebrafish differ significantly from humans and other laboratory animals in many respects, such as the complexity of the nervous system, they serve as a kind of "gatekeeper."

"If we expose zebrafish to a drug or chemical and we observe adverse effects, that serves as a red flag and alerts us to take a closer look for toxicity," he says FDA

Find this and other Consumer Updates at *www.fda.gov/ForConsumers/ConsumerUpdates*

Sign up for free e-mail subscriptions at *www.fda.gov/consumer/consumerenews.html*