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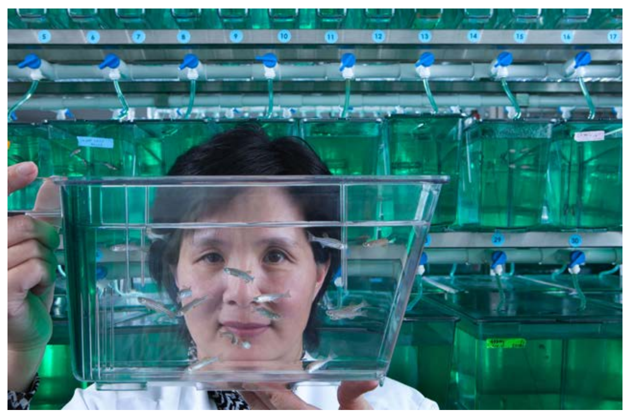
Go Zebra Fish

BY JOSHUA TOMPKINS | FEATURES | *leave a comment »* SUMMER 2010

This is no fish story: the tiny striped zebrafish is taking the research world by storm.



Hidden away in a balmy, windowless room on the fifth floor of a research building on the Cedars-Sinai campus, thousands of fish are swimming tirelessly in small plastic aquariums. They dart in one direction for about two seconds and then change course, as if ricocheting off an invisible barrier. Each fish seems to move separately, yet no two ever collide. Hundreds of tanks of various sizes are arrayed on tall racks like books on library shelves. They bear none of the fluorescent splendor of traditional aquariums. There is no coral or speckled gravel or plastic plants gently swaying in the current—just two-inch silver fish sporting five navy-blue stripes running from head to tail.

They are zebrafish, native to Himalayan streams and a popular choice among aquarium hobbyists because they are good-natured and easy to care for. They eagerly munch on brine fish and play well with other fish. It’s hard to believe that this small, mundane tropical fish, frequently sold under the trade name zebra danio, is quickly becoming a favorite of the scientific world as the best animal to utilize for genetic studies.

Indeed, zebrafish are rapidly occupying a key position in the pantheon of disease-model organisms. In the past decade, the number of academic papers based on zebrafish research has increased more than fortyfold. In April, scientists at India’s Institute of Genomics and Integrative Biology completed the sequencing of a zebrafish genome, and more than 5,000 scientists in 32 countries are now conducting zebrafish-based research.

Cedars-Sinai endocrinologist Ning-Ai Liu, MD, PhD, has devoted the last eight years of her career to studying the zebrafish pituitary gland. On a photograph of a spherical embryo, she points at a cluster of cells cordoned off by a thin membrane. “It is visible 32 hours after fertilization,” she says. Her research using the tiny striped freshwater fish could lead to the development of therapeutic drugs for treatment of human pituitary hormonal dysfunctions, cancer, and Cushing’s disease.

Genes serve as the blueprints for the thousands of proteins synthesized into cellular molecules— ranging from antibodies to collagen. By tugging at and unraveling this Byzantine system, scientists are slowly connecting genes to their respective functions, the same way a new homeowner might flick fuse-box switches on and off to discover which part of the house is controlled by each circuit.

Before geneticists discovered zebrafish, however, a blind spot had formed in the effort to decode human genes by experimenting with animals. Scientists working with swarms of fruit flies could blitz them with mutation-inducing chemicals and quickly sort out the effects on body structure and function—for example, smaller wings, or blindness— but many of the affected genes had no obvious human counterparts. Scientists studying mice, whose DNA matches humans’ more closely, were stymied by the animals’ comparatively low breeding capacity and lengthy internal gestation. Of key interest were genes that guide the developing fetus, which cannot be readily scrutinized while nestled in the womb.

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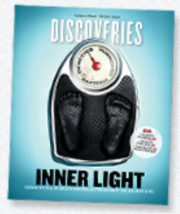

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In the late 1960s, George Streisinger, a molecular biologist at the University of Oregon, realized the solution might be swimming in his home aquarium. Unlike fruit flies, zebrafish are vertebrates whose development and physiology are surprisingly parallel to ours (see illustration). Like humans and other higher animals, they have a lymphatic system and an adaptive immune system that remembers and guards against specific viruses to prevent reinfection. They also have the capacity to regenerate organs and structures such as the heart, fins, and retinas. Zebrafish have 25 chromosomes as compared to our 46, but scientists suspect the fish have about the same number of genes—some 30,000—in their DNA. Roughly 70 percent of the zebrafish genome is identical to ours.

Some of the same qualities that made zebrafish such an evolutionary marvel are most helpful to researchers like Dr. Liu, especially those frustrated by the laborious and expensive process of mouse-based research. Female zebrafish lay a steady supply of more than 10,000 eggs per year, versus the two or three dozen pups a female mouse might bear in a lifetime. Zebrafish embryos develop externally to the mother, and display all major organs after just 24 hours; their transparency facilitates observation via the microscope. Scientists can watch in minute detail how the vertebrate coming-of-age play unfolds in a sphere smaller than a soap bubble.

Each tank in Dr. Liu's aquarium lab includes males and females, and just as they are tireless swimmers, they also are tireless breeders. Females are trimmed in silver; males in gold. Eggs laid by the females are immediately swept from the tank by the recirculation system, which leads to a huge central tank where the water is oxygenated and purified. When Dr. Liu actually requires fertilized eggs, she places a male and female overnight in a small plastic Tupperware®-style container. After the female expels eggs—several hundred, typically— from her oviduct and they settle on the bottom of the container, the male hovers over them and releases a wispy cloud of spermatozoa, only a small fraction of which penetrates the eggs. Liu collects the fertilized eggs the next morning. "We can easily house 5,000 fish and process 8,000 embryos a month," she says.

Tall and slender, Dr. Liu remains fresh-faced and full of energy in the sweltering humidity of the fishlaboratory. “She is highly intelligent and scholarly,” says Shlomo Melmed, MD, dean of the Medical Faculty. “Very self-effacing and exceptionally creative.”

Born in Shanghai, Dr. Liu received her medical degree from Shanghai Medical University. She moved to the United States in 1986 and earned a PhD in biochemistry from Boston University. After residency at the Medical College of Georgia, she came to Cedars-Sinai in 2001 as a clinical fellow in endocrinology. When Dr. Melmed, a renowned endocrinologist, suggested she investigate pituitary disorders by working with zebrafish, she was skeptical. “I wasn’t sure if zebrafish even had a pituitary gland,” she says. Now the fish is practically family: Her husband, Shuo Lin, also studies the species in his role as professor of biology at UCLA.

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In zebrafish, humans, and other vertebrates, the pituitary is the body's master gland, secreting hormones that govern growth, metabolism, excretion, ovulation, and other core functions. Pituitary dysfunction, which is often hereditary, causes many familiar diseases, including hormonal failure and infertility. Insufficient production of growth hormone can result in dwarfism; excess production can lead to acromegaly. Many of the world's tallest and shortest people owe their stature to their wayward pituitary glands.

Some pituitary diseases are caused by a tumor on the gland. One form of tumor triggers the release of a hormone (ACTH) that compels the adrenal glands to secrete the steroid hormone cortisol. Cortisol, in turn, elevates blood sugar levels, and a glut can cause weight gain, diabetes, osteoporosis, and heart disease, among other problems. The tumor condition is called Cushing's disease, named after Harvey Cushing, the American surgeon who, in 1932, linked the symptom to the pituitary. Treatment options are few and unattractive. Many pituitary tumors are too invasive for successful surgical removal, leaving doctors to prescribe cortisol-inhibiting drugs that are not always effective. Patients with untreated Cushing's disease often exhibit a cherubic appearance known as "moon face," due to the deposition of fat in the cheeks.

Zebrafish can get Cushing's disease, too, as Dr. Liu proved by creating a strain of zebrafish predisposed to developing the pituitary tumor. Starting at three months old, the fish begin to present symptoms such as diabetes, heart disease, and liver dysfunction. They can be spotted by the telltale bulge on their undersides from the resulting enlargement of their struggling heart.

Engineering a zebrafish version of Cushing's disease is the jumping-off point of Dr. Liu's work. For clinicians — Liu sees patients once a week at her pituitary clinic—the most promising avenue of zebrafish research is the field of drug discovery. This is the area of science where zebrafish unequivocally trump mice, which are too expensive to maintain in very large numbers. "If we're talking about 500 mice, that's a lot of animals," Liu says. As a result, scientists are typically forced to attempt candidate drugs on mice one at a time, in a tedious loop of trial and error. But with zebrafish, the process can be done rapid-fire. "We put the embryos in a dish and throw in 300 potential drugs," she says. Any drug that has an effect is singled out for further testing. Meanwhile, another 300 compounds are loaded into the zebrafish wells.

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Dr. Liu says she is just now beginning to test drugs and plans to test thousands of compounds. “I am hoping for something completely surprising to come out of this process,” she says.

She developed a strain of zebrafish predisposed to pituitary tumors by tricking a gene called the pituitary tumor transforming gene (or PTTG) into producing too many cell growth proteins, which in turn causes the formation of an abnormal tumor. Dr. Liu points to a row of tanks at her knees: They contain the fish with hyperactive PTTG genes. They look no different from the fish in the other tanks. They act the same, too: Dart, bounce, dart, bounce. She will soon begin screening for therapeutic drugs using thousands of zebrafish embryos.

Some scientists have suggested that zebrafish will render mouse-based research obsolete, but Dr. Liu balks. “Zebrafish will never replace mice,” she says. “It’s not a mammalian model.” Instead, she explains, zebrafish studies will serve as a proving ground where the best candidate drugs and genes for subsequent human studies will emerge. Find a drug that cures tumors in zebrafish? Try it on mice. If successful, it could eventually reach human trials. Zebrafish simply provide a more expedient starting point.

“This approach is going to be very important for a whole host of diseases, including metabolic disorders as well as heart dysfunction, diabetes, and cancer,” says Dr. Melmed. “The potential is there, and most of the big drug companies have large zebrafish discovery programs.”

That said, the transparency that zebrafish bring to genetic study is nothing short of revolutionary. Dr. Liu has also spliced an extra gene into her pituitary-compromised zebrafish that creates a fluorescent protein. In the glare of ultraviolet light, the pituitary cells responsible for the cortisol overproduction flare like a cat’s eyes. Zebrafish bearing variations of the same Day-Glo feature may light up other organs or even the bloodstream itself. The tiny fluorescent heartbeat of a zebrafish embryo can be studied using a specially equipped digital microscope.

When asked how long she thinks the screenings for new drugs will continue, Dr. Liu imposes no deadline—there are thousands of compounds to test. “The immediate goal is to find molecules that can treat Cushing’s disease,” she says. “That would be a huge accomplishment.”

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