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Zebrafish genome to be sequenced

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Gail Vines

The genome of the zebrafish *Danio rerio* is to be deciphered by a dedicated team at Britain's Sanger Centre. The project to sequence the zebrafish's 1.7 x 109 base-pair genome - about half the size of that of the mouse or human genome - is expected to take three years. As with all projects undertaken by the Sanger Centre, the sequence information will be released rapidly and made available to researchers without cost or restriction.

Researchers will then be able to use this model organism to "fill in the gaps" in biological processes already under investigation in yeast, flies and worms, says Professor Christiane Nüsslein-Volhard from the Max-Planck Institute in Tubingen, who received a Nobel Prize in 1995 for her work on *Drosophila* and in the past decade has turned her attention to zebrafish. Even more importantly, perhaps, the fish "will make an enormous contribution to our understanding of organ formation," she says. "Zebrafish is the ideal organism to study the function of human genes."

Insights into many human diseases are likely to emerge from research into the zebrafish. Already, there is some "very promising stuff," says Nüsslein-Volhard. "Most human genes will have homologues in fish," she suspects.

But why the zebrafish? Its ability to adapt to laboratory life is part of the answer. Named for its striking black and white stripes, the zebrafish has long been a favourite with tropical fish fanciers, who recommend it as ideal "beginner's fish". Adapted to life in the Ganges, this robust fish breeds prolifically and reaches maturity in just a couple of months. Its potential as a laboratory species was first recognised in the mid 1970s by the late George Streisinger of the University of Oregon, who assembled a team of neurobiologists to study phenomena such as axon guidance in the developing nervous system of zebrafish embryos.

These embryos "are really wonderful, they are the zebrafish's best feature," says Nüsslein-Volhard. Big and completely transparent, "you can look inside as they start developing in front of your eyes," she explains. "In 48 hours, they can swim." Best of all, and what makes the zebrafish different from all other vertebrates, she says, is that large-scale mutagenesis is feasible.

Since the late 1980s Nüsslein-Volhard's group has amassed more than 1000 developmental mutations in these embryos, constituting a research resource that is unique among vertebrates. Each mutation holds vital clues to the functioning of genes in key biological processes but, so far, not more than 50 zebrafish genes have been cloned. "For the zebrafish we have the mutations but don't have the genes, whereas in humans we have the genes but don't have the mutations," she says. Sequence the zebrafish genome, however, and the zebrafish can stand as the Rosetta Stone for researchers struggling to find meaning in the vast human genome.

As a vertebrate equipped with organs and tissues comparable to the human - heart, kidney, pancreas, bones and cartilage - the zebrafish can provide insights that fruit flies or nematodes never will. For instance, Philip Ingham and his colleagues at the MRC Intercellular Signalling Group at the University of Sheffield, UK, have used zebrafish to unravel the 'hedgehog' signalling pathway. The results suggest that in all vertebrates hedgehog signalling plays a key part in muscle development, specifying fibre types of muscle cells. Mutations in one particular gene, *sonic hedgehog*, are associated with one of the most common forms of human birth defect, holoprosencephaly, in which only a single eye develops in the

centre of the forehead. Mutations that affect the signal transduction pathway downstream are implicated in basal cell carcinoma, a form of skin cancer.

Worldwide, some 250 laboratories are now using the zebrafish to study developmental processes in most of the vertebrate body's major organ systems.

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