What fish can teach us

Understanding the zebrafish's remarkable regenerative ability may help human organ research, **Nyssa Skilton** writes

They may seem like an unassuming tropical aquarium fish, but zebrafish could hold the secrets to exploit the powers of human regeneration.

Scientists around the world use zebrafish as a kind of laboratory rat because they have an extraordinarily fast rate of development, which is conveniently on show to the outside world. Zebrafish embryos grow most of their major organ systems within about 24 hours – it can do in three days what a human embryo does in three months – and researchers can watch this early development in intricate detail as the transparent embryo develops outside the mother's body.

The tiny fish also have remarkable regenerative capabilities. Nearly every organ system, including the spinal cord, can undergo some form of regeneration.

Professor Peter Currie is the deputy director of the Australian Regenerative Medicine Institute at Monash University in Melbourne, which runs the largest zebrafish laboratory in the southern hemisphere.

The $5.4 million aquarium, which opened in 2008, contains roughly 60,000 fish, housed in thousands of tanks packed in floor-to-ceiling shelves.

Currie says you can basically cut a zebrafish in half and it will regenerate.

"They're able to regrow many of the organ systems that we can't in an injury setting," he says.

"The classical one people often point to is the heart. In zebrafish you can resect up to a third of the ventricle of the heart and over a course of a month that tissue, the cardiomyocytes of the heart, will regrow to a point where it's practically indistinguishable to what it was before the injury occurred."

Currie describes what happens to a zebrafish heart after a piece is cut out of it. Immediately a tiny scar forms, just like it would in a human, to seal the wound and stop the flow of blood. This is normally where the process stops in humans and the tissues around the site begin to die. The zebrafish, however, gradually removes the scar in the early phase and replaces it with new muscle cells. Over about a month, the heart grows back to its previous condition.

The origin of cells that generate the growth of the heart in zebrafish is controversial among scientists.

Some believe there are stem cells resident in the heart, while others think the cells injured at the site of the wound may, triggered by the injury, turn into stem cell populations.

"If we can understand why the heart tissue in a fish is able to regenerate so effectively, we can engender a similar property in ourselves," Currie says.

"Obviously the major cause of morbidity in the Western world would be solved, because basically our inability to recover from heart attacks and myocardial infarctions is one of main reasons that people die." Strangely, zebrafish are genetically similar to humans. Although the zebrafish genome is only about half the size of that of the human in terms of DNA quantity, the genes share many characteristics.

The fish have similar organ systems to humans, similar immune systems and even the genes that make up the brain are alike.

"It's rather a sad or a positive fact of life, depending on which side of the fishy fence you're on, that actually we really are just modified fish. The fossil record's pretty clear on that. All vertebrates evolved from fish ancestors and it's no surprise that many of the vast majority of genes that make up the vertebrate have their origins in fish."

Currie leads a research group at the Australian Regenerative Medicine Institute which studies injury and disease models in zebrafish that reflect human muscle disorders. Fish are particularly useful subjects in this area because they consist of about 90 per cent muscle.

The researchers cross-breed numerous zebrafish to try to find mutations in the fish that produce diseases similar to those in humans. They examine how the fish react to the mutations and work to understand the cells responsible for regeneration. They have found zebrafish have stem cell compartments in the muscle, which seem to be able to produce and regenerate tissue more effectively than humans.

Ultimately, they want to understand the genes that can produce the "super stem cells" that regenerate all the different systems within the zebrafish.

One of the genetic models the researchers use is the most common muscular dystrophy, Duchenne muscular dystrophy, an inevitably fatal genetic disease which leads to progressive muscle weakness in males.

The disease causes the muscles to go through cycles of degeneration and regeneration until finally the muscle stem cells are exhausted and no longer replenish. Those with the disease often die in their late teens.

Zebrafish with the disease model have similar early muscle loss, but they survive much later into what's considered the adult phase of their lives.

"We believe it's the ability of muscle cells to continually replace themselves and the zebrafish might underlay aspects of their recovery from this very catastrophic early muscle wasting syndrome to something a lot less debilitating," Currie says.

Zebra fish have helped scientists shed light on various diseases from Alzheimer's to leukaemia.

In 2008, United States researchers at Children's Hospital Boston created a zebrafish that was transparent through its entire life. The eerily see-through fish offered scientists a direct view into its internal organs so they could observe processes like blood production after a bone-marrow transplant in a living organism.

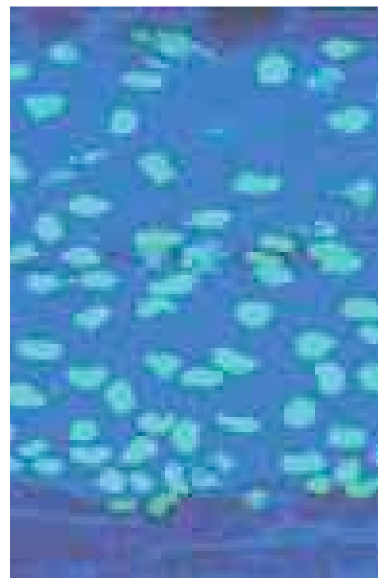
Currie says the embryos themselves are "optically exquisite".

"You can see every cell in the developing embryo without any intervention. You can see everything occurring from one cell, right through to the formation of complex behaviours in three or four days in a fish – it's really quite astounding."

Scientists can use intricate imaging techniques to better understand aspects of embryonic development, such as how stem cells come into being in the embryo, where they are activated and where they migrate to.

But there is still much to learn from the tiny fish, particularly about its skills in regeneration. Scientists are yet to understand why the fish have retained their abilities to regenerate, while humans have not.

"The real hope is that it could be something relatively straightforward, to genetically tweak a system that already exists in us, and for some reason is not functioning very well, and just unlock its potential more fully," Currie says. "That's really what everybody hopes."



Clockwise from top left: Professor Peter Currie, the deputy director of the Australian Regenerative Medicine Institute, which runs the largest zebrafish laboratory in the southern hemisphere; muscle stem cell; zebrafish embryo; zebrafish; and fish tanks at the zebrafish research facility in Melbourne.

Photos: Monash University

■ This is the second instalment of a three-part series on regenerative medicine in *Times 2* Science. The final article, which will look more closely at human regeneration, will appear next Monday.