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RESEARCH NEWS

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Fish Show How to Fix a Broken Heart

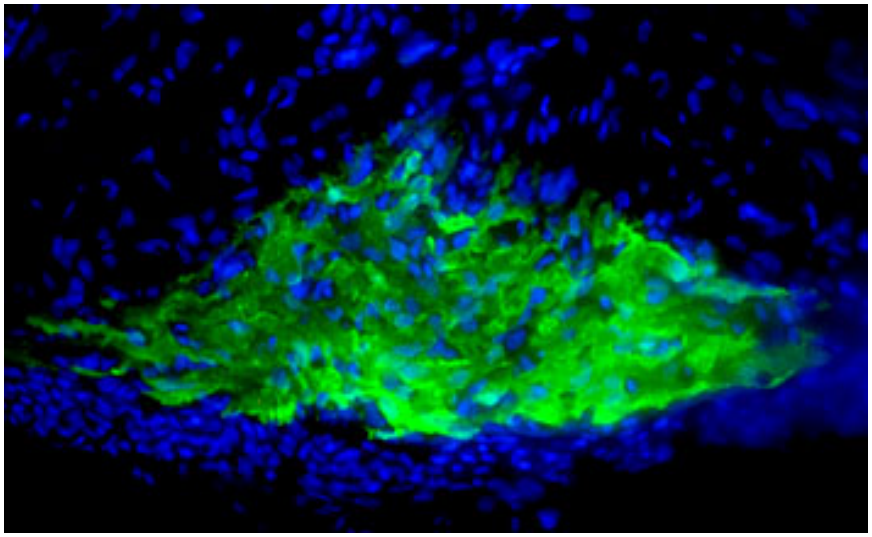

Image Title: Regenerating cardiomyocytes in the ventricle of a zebrafish 30 days after amputation. Green fluorescent protein appears in cells that are expressing the *gata4* gene. The nuclei of all cells are stained blue. - Kazu Kikuchi

After a non-fatal heart attack, a damaged human heart does its best to patch itself up by forming a scar. But how much better would it be if that patch were made up of healthy, fully functional heart muscle rather than scrappy, stiff scar tissue?

Some animals, such as zebrafish, have the natural ability to repair their own injured hearts. Over the last decade, scientists have become increasingly interested in the amazing regenerative capacity of such organisms, as they search for new ways to prompt human hearts to repair themselves. Using advanced genetic tools, Howard Hughes Medical Institute researchers and their colleagues now have identified key cells involved in zebrafish heart regeneration and begun to decipher the instructions the cells use to carry out their repair work.

Kenneth Poss, an HHMI Early Career Scientist at Duke University Medical Center, led the research, which is reported in the March 25, 2010, issue of the

journal *Nature*. Coauthors on the paper are from Duke University Medical Center, Brigham and Women's Hospital, the University of California, San Francisco, and Cornell University.

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> **- Kenneth D. Poss**

Poss says scientists are pursuing two basic paths to regenerate human heart muscle. One involves giving the heart the instructions for repair, along with a batch of fresh cells -- typically stem cells -- capable of carrying out those instructions. An alternative approach, he says, is to give the instructions to cells that are already present and try to teach them to regenerate. He and his colleagues, including Kazu Kikuchi, who is the first author of the *Nature* publication, have identified an important population of cells that participate in zebrafish heart regeneration. They believe they now have new perspective on which cells might be "taught" to regenerate in human hearts.

To arrive at their findings, the researchers stimulated zebrafish heart regeneration by cutting off part of the ventricle. Then they borrowed techniques from developmental biology and stem cell research that allowed them to track the activity of particular cells and their progeny over time.

"We found that a population of cardiomyocytes – heart muscle cells -- on the periphery of the injury site becomes activated to carry out a specific genetic program," Poss says. "We don't know everything about the program, but at least one of the genes that becomes activated is a factor called *gata4*. When the cells turn on this gene, heart muscle cells near the site begin to divide and integrate into the gap to build a new wall of heart muscle."

But is that wall just a static structure, or does it work like healthy heart muscle? Results showed that by about two weeks after injury, electrical conduction had been restored, with cells of the new wall contracting in sync, as healthy heart muscle cells should.

The researchers went on to investigate whether heart muscle could be regenerated even after scarring had occurred, an important question if results are to be translated to human hearts, where scarring is the natural response to injury. Zebrafish don't typically repair injuries with a scar, but Poss and colleagues developed a way to induce scar formation and found that while regeneration didn't completely erase the scar, as they hoped it might, some

regeneration did occur in the wounded area.

"We saw activation of *gata4*, and in several cases muscle was built around the scar -- so there seems to be some regenerative signal even in the presence of scar tissue," says Poss. "As we identify these signals, we're hopeful that we or other researchers can use what we learn to help people with severely injured, scarred hearts."

Now that the researchers have found a way to follow heart regeneration "with a better pair of glasses," as Poss puts it, they plan to study the process in even greater detail by searching for molecules or manipulations that enhance or block it.

"We're also interested in the environment of the zebrafish heart that allows these cardiomyocytes to be activated," Poss says. "We have been studying different heart cell types that are not muscle cells, investigating how those might be involved in initiating or facilitating the regeneration process. We wonder whether the non-muscle cells of the heart are providing a unique environment for this to happen."

Another logical step would be to try to induce regeneration in a non-regenerating system, such as a mammalian heart.

"We don't have plans to work with human cells yet, but as a first step we may collaborate with groups that work with mice," says Poss.