The salamander that eats its siblings' arms could one day help you grow a new one

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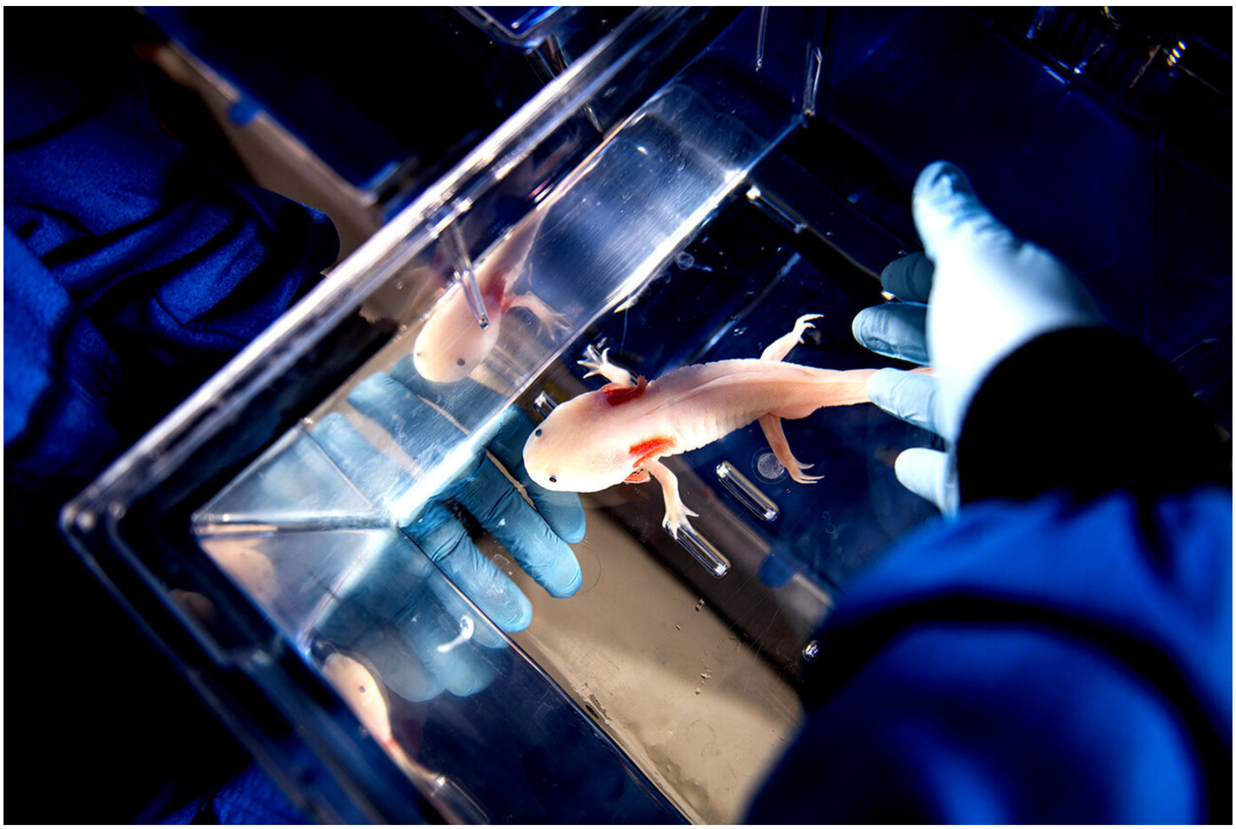


James Monaghan, an associate professor of biology, studies the mechanisms that allow axolotls to regenerate parts of their body. Credit: Matthew Modoono/Northeastern University

Imagine you're a smiley-faced, feathery-gilled Mexican salamander called an axolotl. You've just been born, along with hundreds of brothers and sisters. But salamanders like you live in the wild only in one lake near Mexico City, and that habitat isn't big enough for all of you. There's not enough food. Only the strongest can survive. What do you do?

If you're an axolotl, you have two choices—eat your siblings' arms, or have your arms eaten.

But even if you are the unfortunate victim of this sibling violence, not all hope is lost. In a few months, you'll grow a whole new arm—bones, muscle, skin, nerves and all.

"It's pretty gruesome, but cannibalism is a possible reason why they grow their arms back," says associate biology professor James Monaghan. His lab studies regeneration in axolotls, a peculiar species that can grow back limbs and other organs to various degrees.

"When an injury occurs, some cues are released in that animal that tells cells near the injury to go from a resting state into a regenerative state," Monaghan says.

His lab is trying to figure out what those cues are, and how we might induce that response in humans, who have very limited regenerative abilities.

"Humans are notoriously bad at regenerating," Monaghan says. After we're done growing, the genes that tell our cells to grow new organs are turned off.

"That's a good thing because otherwise it'd be chaos," he says. No one wants to spontaneously grow an extra finger.

"Axolotls can turn back on those genes that we turn off permanently," Monaghan says.

Understanding the specific mechanisms that induce regenerative responses in axolotls is no small task since axolotls have the largest genome ever sequenced.

So far, the lab has identified one molecule, neuregulin-1, which is essential for regeneration of limbs, lungs, and possibly hearts.

Axolotls are unique because they can regrow fully developed organs at any stage of their lives, says James Monaghan, an associate professor of biology. Maybe one day this same process can be induced in humans. Credit: Matthew Modoono/Northeastern University

"When we removed it, regeneration stopped. And when we added it back in, it induced the regenerative response," Monaghan says. "I'm not saying it's a golden bullet for inducing regeneration in humans, too, but it could be part of the puzzle."

A lot of researchers study limb regeneration in axolotls. But Monaghan's lab is interested in extending this research to other organs, as well.

"When you think of the human condition, most of our issues with disease are with internal organs," Monaghan says.

Take retina regeneration, for example. Monaghan says we can either learn the process axolotls undergo that allows their specialized cells to return back to developmental cells, and then mimic that process in human eyes. Or, we can learn which elements of the axolotl enable their cells to behave this way, and then add those elements to human stem cell therapy.

To test the latter, Monaghan has teamed up with a Northeastern associate professor of chemical engineering, Rebecca Carrier, and her lab to figure out the best way to transplant mammalian retinal cells using molecules found in the axolotl.

In the experiment, Monaghan and Carrier used pig eyes, which are similar to human eyes. When they transplanted stem cells from the retina of one pig into the retina of another, 99 percent of the transplanted cells died. "Something's missing," Monaghan says. "The cells don't have the right cues."

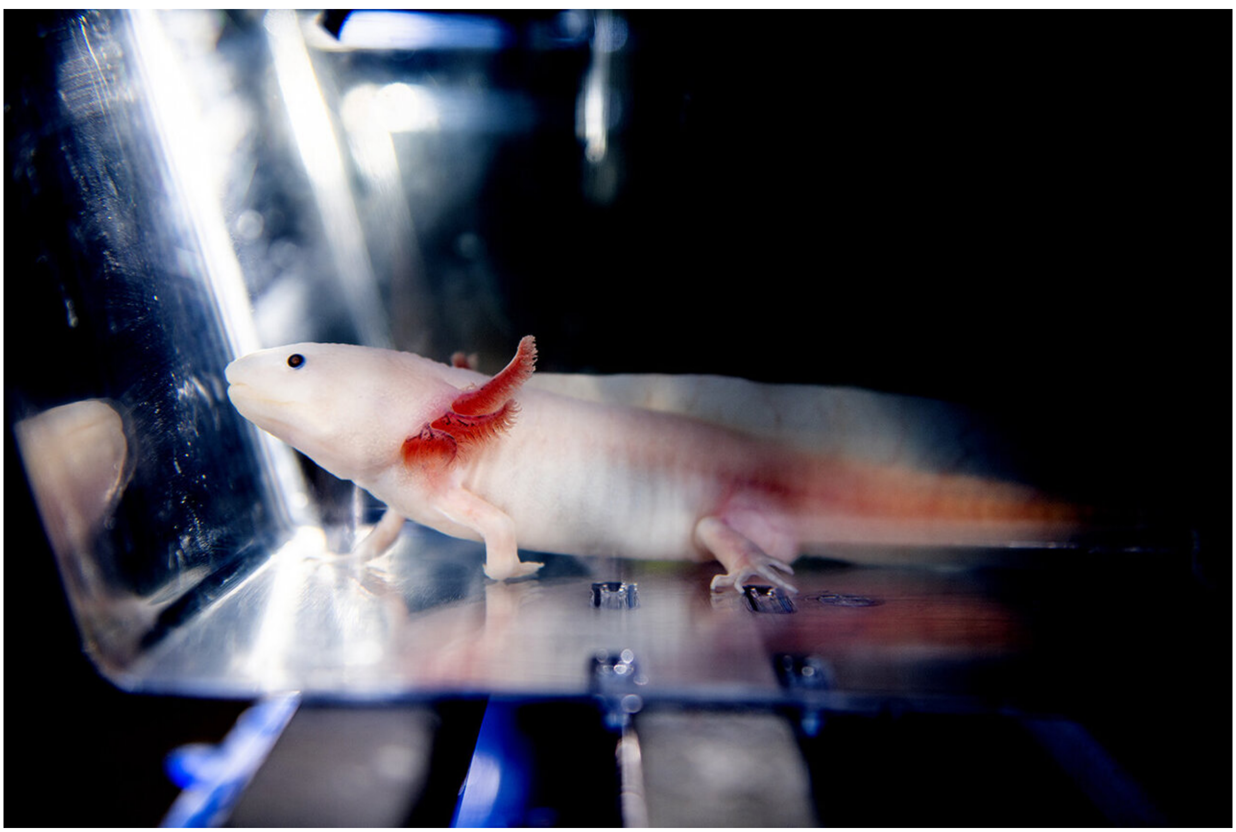
But when Carrier and Monaghan injected those same pig stem cells into the axolotl eye, fewer cells died. "They were much happier," Monaghan says. "There's something in the axolotl retina that the mammalian cells like."

One reason axolotls are so good at receiving transplants is because, unlike humans, they don't have a learned immune system, meaning they can't distinguish between themselves and foreign entities.

"It's really easy to do grafts between animals because the axolotls can't tell that the new tissue isn't theirs," he says. "They don't reject it like we might."

An obvious example of this can be seen in axolotls that are genetically modified with a green fluorescent protein found in jellyfish. These naturally white axolotls glow neon green in certain lighting.

"With this we can ask really basic questions, like do cells change their fate when they participate in regeneration?" Monaghan says.



Credit: Matthew Modoono/Northeastern University

For example, if Monaghan grafts muscle tissue from a green fluorescent animal onto a white axolotl and then that axolotl regenerates, does the axolotl grow green muscle? Do its bones glow green, too? What about its skin?

Researchers have found, however, that cells don't actually change. Green muscle yields green muscle only.

The axolotl isn't the only animal that can regrow organs. Starfish, worms, frogs, and other species of salamanders can also regenerate. But axolotls are special because, unlike other animals, they can regrow organs that are just as robust as the originals, no matter how old they get.

For example, tadpoles can regenerate limbs. But once they undergo metamorphosis and become frogs, "they can only regrow a spike," Monaghan says. "They lose the ability to grow back their digits."

The axolotl's ability to fully regrow organs, even as it ages, could be partially due to its perpetual juvenile state. Axolotls, unlike most other amphibians, don't undergo metamorphosis naturally, which means they never technically reach adulthood, even though they can reproduce. This condition is called neoteny.

"Axolotls come from a species that used to walk on land," Monaghan says. They do have legs, after all. "But some mutation occurred that keeps them in the lake and from reaching adulthood."

To test whether their neotenic state is responsible for their ability to regenerate, Monaghan took a group of axolotl siblings and induced metamorphosis in one half by exposing them to thyroid hormones, a chemical that flips on the maturity switch in these amphibians. The other half was kept in the juvenile state.

In the experiment, the juveniles regenerated normally, but all of their adult siblings regenerated slower than usual, and had deformities in their regrown limbs.

"There is some association with neoteny and the ability to regenerate," Monaghan says. "But it's not the main factor."

That main factor is yet to be discovered. But even though some of this might sound like science fiction, "you already made an arm once," Monaghan says. "If we could just learn how to turn back on those programs, our bodies might do the rest of the work."

Provided by Northeastern University

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