

Regenerating limbs

"Salamanders - our distant relatives - give us important clues about what we should be testing, and what we learn from them keeps us on the right path."

Jessica Whited, PhD is an assistant professor of orthopedic surgery. Her research group at Harvard Medical School and Brigham and Women's Hospital is dedicated to exploring the basic biology of salamander limb regeneration.



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Could we regrow a limb after amputation? Jessica Whited investigates.

- HSCI researcher Jessica Whited, an expert in developmental biology and regenerative medicine, is exploring the possibility of regrowing lost limbs
- Whited studies a type of salamander that can regenerate its limbs throughout its life, so she can achieve her goal of regrowing human limbs after patients undergo amputation.
- By investigating how the salamander heals wounds without scarring, Whited wants to help people regenerate damaged tissues.

In my lab, we study salamanders – axolotls – because they have this amazing ability to regenerate their limbs throughout their entire lives. To me, what makes this so remarkable is that human and salamander limbs have very similar types of cells, with similar shapes. So why can't humans spontaneously regenerate limbs following amputation?

The scientific question I am exploring is how salamanders do this.

How can this eight-year-old animal get injured in the wild, then regrow a structure as complicated as a limb?

They don't just regrow some "arm-type" cells – they grow a perfect match. So if the animal loses only a hand, it will regrow just a hand. If it loses a whole arm, it will grow back the whole arm (the right way around).

What pathways do salamanders activate to call up the right cells and direct the repair? I want to find some answers, because I think we could make human limb regeneration a reality.

Why do we scar, instead of regenerating tissues?

Animals that are master regenerators, like salamanders, don't scar. If they get cut they just heal, and you can't tell where the cut happened.

One reason adult humans can't do this is because our healing process favors speed – we form scars so we can extinguish the problem quickly.

This ability might have evolved in mammals at a cost: losing the regenerative prowess that ancient animals might have shared.

Scientists have thought for a long time that scarring prevents true tissue regeneration – but

it's only now that we can test it. We have the right tools – like the reference axolotl genome – to see what happens in detail: which cells are activated following amputation, how they counteract scarring, and what they do to promote a "pro-regenerative" environment.

We can also see exactly what happens to the cells that are activated, and ask questions like:

- How long can these stem cells last?
- How many times can the animal call them up to repair the tissue?

Once we have some answers, we can start to explore the

balance between scarring and regeneration in more detail. That's important not just for regrowing limbs, but regrowing any damaged tissue: heart, spinal cord, just about every one you can imagine.

Why did you choose regenerative medicine research?

I'm often asked how I ended up in this career, and it's a good question.

There were no doctors or scientists in my family, but my mother was really into nature and the outdoors. We collected butterflies together, and that's how I first got interested in biology.

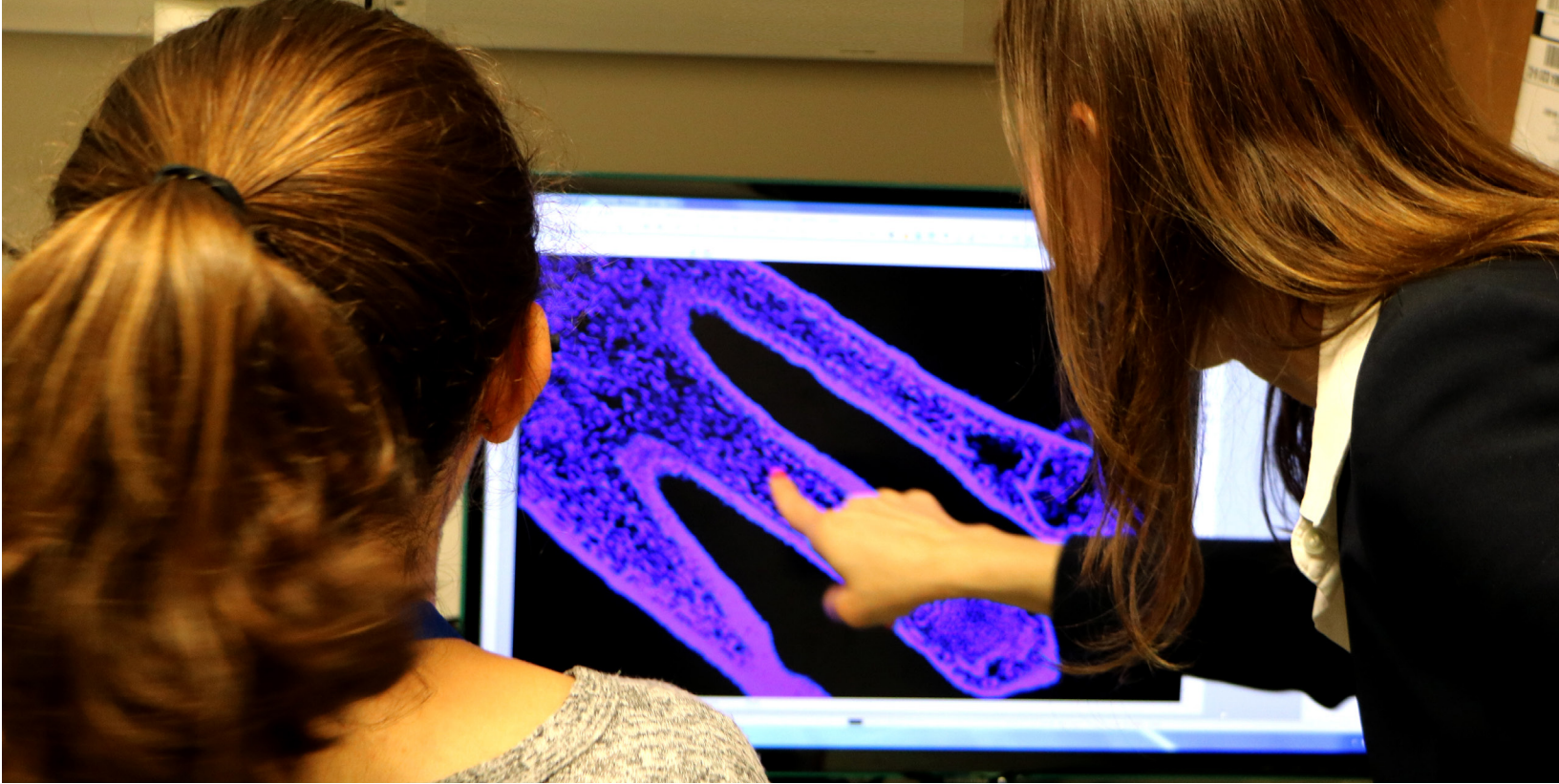
In college I studied both philosophy and biology, and pursued a PhD at MIT on the neurobiology of fruit flies. I was using genetics and developmental biology to understand how this fruit fly made its eye and its brain.

But then I was consumed with curiosity about exactly how fruit flies keep all their cells in the right spot after they're born, and how they put everything back in place after they're injured.

My postdoctoral mentor, Cliff Tabin, gave me an incredible amount of excitement and hope

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Jessica Whited looks carefully at a high-resolution microscopy image of an axolotl salamander hand, together with one of her Ph.D. students, Margalit Mitzner. Mitzner is researching the role of a secreted signaling protein in limb regeneration, as this particular protein has a counterpart in humans.

when he took me into his lab, even though I was jumping from invertebrates (a new generation of flies every two weeks) to axolotls (a year between generations). During my job interview he said, "Well, if you want to work on axolotls, this is going to be a really long postdoc."

That made me feel good, because it meant he accepted the challenges that were in front of us.

It wasn't until I'd built my own confidence, though, that I was ready to start a lab. This topic is so compelling. I felt that if I could start a whole lab dedicated to understanding regeneration, I could get people to join me who would want to work on it. And that's just what happened.

Everyone in my group is really dedicated, and totally focused on figuring out one part of this big question.

What is your dream for improving human health?

Humans have more regenerative tools than we might think, but our biology is so complex that it's easy to lose our way, and find ourselves going down rabbit holes.

Salamanders – our distant relatives – give us important clues about what we should be testing, and what we learn from them keeps us on the right path.

In the future, scientists should be able to treat people who've had an amputation by giving them therapies that stimulate an innate response. That's my dream.

Selected publications, Whited group

Johnson K, et al. (2018) Systemic cell cycle activation is induced following complex tissue injury in axolotl. *Dev Biol.* 433:461-72

Natarajan N, et al. (2018) Complement receptor C5aR1 plays an evolutionarily conserved role in successful cardiac regeneration. *Circulation* 137:2152-65

Payzin-Dogru D and Whited JL (2018) An integrative framework for salamander and mouse limb regeneration. *Int J Dev Biol.* 62:393-402

Bryant DM, et al. (2017) Identification of regenerative roadblocks via repeat deployment of limb regeneration in axolotls. *NPJ Regen Med.* 2:30

This article can be found on the HSCI website: www.hsci.harvard.edu