New Methods for Regrowing Nerves could Reverse Blindness

Two millimeters of nerve fiber growth revolutionize neuronal regeneration

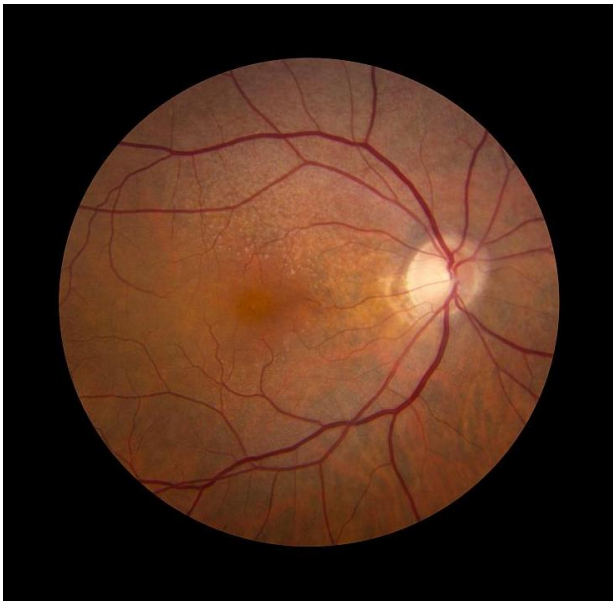
By Anastassiya Kim

Growing new organs, watching wounds heal in front of your eyes, and regrowing completely functional limbs. Regeneration sounds like a superpower from one of those sci-fi books, but it's very real. Many living organisms, including starfish, geckos, and worms, regrow and repair injured parts. Even humans can regenerate some organs. For example, our skin sheds dead cells and replaces them with new cells every day. In fact, if you have ever broken a bone, you will know that in a healthy body bones can flawlessly regenerate on their own. But what does regeneration have to do with treating blindness?

The problem is that some cell types cannot regenerate, such as neurons in the central nervous system (CNS). And one important nerve in the CNS is the **optic nerve**.

The optic nerve is a cable of nerve fibers that carries visual information, from the eye to the brain. According to Larry Benowitz, Professor of Neurosurgery and Ophthalmology at Harvard Medical School, any damage to neurons tends to be permanent as their axons can't regenerate and form necessary neuronal circuits.

Optic nerves are like wires in a computer. What happens when you unplug the monitor from the processor? Yes, the screen turns black. In the same way, when the optic nerves that connect the eyes to the brain are damaged, a person sees nothing. This is what causes blindness. However, if we could repair the optic nerve it might restore vision.



The optic nerve grows around the retina. Optic nerve damage is the most common cause of vision loss and remains incurable to this day.

Photo credit: "Retina showing reticular pseudodrusen" by National Institutes of Health (NIH)

Unfortunately, years of continuous research have found that optic nerve regeneration is a nerve-racking task for at least two reasons:

The first reason is the neurons' inability to grow after maturation. Interestingly, neurons are only able to grow during embryonic development. "Scientists have been wondering whether it is possible to reactivate the processes which manifest in the early developmental phase. This could be a way to trigger regeneration in adult neurons," says Sebastian Dupraz, a

postdoctoral researcher working on nerve regeneration at the German Center for Neurodegenerative Diseases.

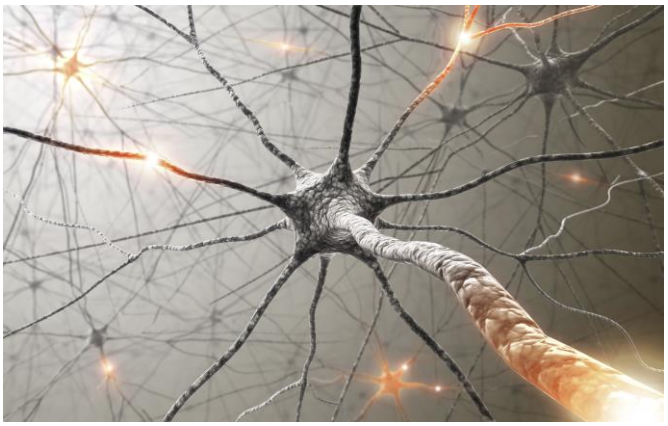
The second obstacle is related to the structures surrounding the nerves, such as **astrocytes**, which are another type of cell usually located beside neurons. Astrocytes provide neurons with structural support and nutrients, but they also grow in number and form a scar-like tissue when neurons are injured. This becomes an obstacle when scientists try to bring the nerve back to life. As the nerve fibers desperately try to grow past the injury site, they cannot penetrate the scar-forming astrocyte tissue.

For many years, different research groups were perplexed at these two obstacles, until 2008 when Dr. Kin Sang Cho and Dr. Dong Feng Chen from Schepens Eye Research Institute in Boston came up with the solution.

In a study published in *Neurochemical Research*, they developed a novel treatment that was effective for tackling both problems at once. They used a substance called **astrotoxin** together with a lithium-rich diet to regenerate damaged optic nerves in mice. Astrotoxin, as the name suggests, is a "toxic" substance. It inhibits the function of astrocytes and helps axons to penetrate the scar tissue. The lithium supplemented diet was incorporated into the treatment to activate hidden growth capacity in the optic nerves.

Cho and Chen's method turned out to be a tremendous success. After eight days of the combined astrotoxin and lithium treatment, they observed robust regeneration up to two mm past the injury site in mice.

Cho and Chen were even more surprised when they spotted many **growth cones** at the ends of the mice's nerve fibers. Growth cones are hand-like structures with numerous thin extensions at the nerve ends. They have a very dynamic nature that makes them branch in response to various stimuli. A growth cone is like a hand that's searching for another hand to grab onto. Observing numerous growth cones was a great achievement for Cho and Chen as it suggested that the mice's optic nerves were ready to potentially restore neuronal connections.



Nerve cells constantly make connections with each other and other cell types. This feature is critical for the function of the nervous system.

Photo credit: "Neuron" by NIH-NCATS.

The two scientists' method was an amazing breakthrough, but the field has advanced over time and presented even more effective methods of nerve regeneration. In 2017, a group of experts at Boston Children's Hospital and Harvard Medical School discovered another mechanism preventing nerve repair in the retina. Dr. Yiqing Li, the lead researcher of this groundbreaking study, noticed that the concentration of zinc ions in the optic nerves increased rapidly soon after an injury. Like astrocyte tissue,

increased zinc concentration is an extracellular obstacle to nerve regeneration. This is due to **amacrine cells**, which intercept retinal neurons and play an important role in vision, but when nerve injury takes place, they release high concentration of active zinc that is toxic for neurons.

Understanding the problem helped the research team to come up with a solution. They used **zinc chelation**, a reaction that removes excess zinc ions from nerve cells, and observed outstanding results. They used two zinc chelators, TPEN and ZX1, and when compared to no treatment after injury, both demonstrated extraordinary levels of axon survival and regeneration. This study was a major development in the field, as zinc neurotoxicity was never considered a factor in nerve regeneration before, according to Professor Benowitz, who also took part in this research.

The two research teams proved that their treatments can revitalize injured nerves. Cho and Chen's treatment of astrotoxin and lithium was one of the early accomplishments in the field. Zinc chelation, a more recent discovery, has proven to be more effective and stays relevant to this day. Nevertheless, the question remains: Can we treat blindness?

Unfortunately, the answer is no. To restore vision, the regenerated optic nerves need to demonstrate full functionality and be able to form necessary connections with other neurons in the brain. "Axons should grow to specific sites at the damaged areas and at the brain, as well, so as to enable the function of specific targets in the brain and making functional synaptic circuits available," says Dr. Nakamura, retinal specialist from The Eye Bank Foundation of Goiás, Brazil. This is something to be done by future research.

Despite the numerous challenges involved in nerve regeneration, experts remain optimistic about the future of the field. Many research teams around the world are working on various strategies to tackle nerve damage, ranging from pharmacological approaches to stem cell therapy. There's always the possibility that right now someone is on the verge of an incredible discovery. Optic nerve regeneration is certainly worth the effort as it may not only restore sight to millions, but also help scientists understand regeneration in other parts of the central nervous system, such as the brain and spinal cord. In this way, a few millimeters of regenerated nerves can become a gateway to the treatment of many serious chronic diseases like Alzheimer's, Parkinson's, Huntington's, and other aging-related pathologies.