When the Eye Learns to Grow Back

The remarkable science of retinal regeneration

What if blindness were not necessarily permanent?

For the millions of people who lose their sight to disease, the world does not go dark all at once. It fades: a face becomes harder to recognise, steps become harder to see, familiar rooms grow harder to navigate. By the time the change is noticed, retinal neurons may already be permanently lost.

The retina is not just tissue at the back of the eye. It is a living circuit, wired with extraordinary precision to turn light into sight. For much of medicine, damage to that circuit has represented an irreversible event: once its cells are lost, the connections they once formed cannot simply be rewired, leaving the resulting loss of vision difficult to reverse.[1]

Then came an unlikely exception: a small freshwater fish known as the zebrafish. Damage a zebrafish's retina and, within weeks, its regenerative machinery is activated. Damage it again, and the process begins anew. A third, a fourth, even a sixth time, its resident repair cells can still re-enter the cell cycle and generate retinal progenitors.[2] Even age does not erase this capacity: older zebrafish retain the ability to regenerate following acute retinal injury.[3] Not only does regeneration occur, but it can do so again and again.

The cells responsible are called Müller glia. In the healthy retina, they quietly support its neurons and help maintain its intricate network. Yet within these seemingly ordinary support cells lies an unexpected capacity for regeneration. Following injury, they can re-enter the cell cycle, acquire progenitor-like properties and generate new retinal neurons.[1,4]

Humans have Müller glia too. The difference lies in their regulation. Human Müller glia do respond to injury, but their response is largely limited to repairing and stabilising damaged retinal tissue rather than producing new neurons themselves.[1] Researchers are trying to understand what prevents humans from tapping into this regenerative potential.

In 2017, researchers at the University of Washington demonstrated what a single molecular switch could do. By activating the gene Ascl1 and modifying the chromatin environment around it, researchers were able to coax adult mouse Müller glia towards a neuronal fate, generating new retinal neurons that integrated into existing circuitry.[5]

The next question was obvious: could the same switch be flipped in humans?

The answer is not yet known. In 2023, researchers began testing this question directly in human cells. Using human Müller glia derived from fetal retinal tissue and retinal organoids - three-dimensional laboratory models of the developing retina - they investigated the effects of ASCL1, the gene researchers had used as a molecular switch in mice.[6] The results offered a tantalising clue: some cells began to acquire characteristics of neurons, including electrical properties associated with immature nerve cells. These findings are promising, but they reveal the scale of the challenge. Producing a neuron is not the same as restoring vision.

The retina is a remarkably precise piece of biological wiring. Its many specialised cell types are arranged in layers and connected in carefully organised circuits. A replacement photoreceptor must not only detect light; it must also pass its signal to the right neighbouring cells. A regenerated retinal ganglion cell must then transmit that information through the optic nerve to the brain.

This is why replacing retinal cells is less like replacing a broken component and more like rebuilding part of a living circuit. Researchers must therefore look beyond a single molecular switch. Combining Ascl1 with other transcription factors has enabled scientists to steer mouse Müller glia towards different retinal neuron subtypes, rather than producing the same cell type indiscriminately.[7] In principle, this could offer a route towards replacing the particular neurons lost in different retinal diseases.

Alternatively, there is another approach: instead of reprogramming cells already within the retina, researchers can bring in replacements from outside it.

Stem-cell-derived retinal cells have already reached human clinical trials. In early studies, researchers transplanted laboratory-grown retinal pigment epithelial cells into patients with Stargardt disease and age-related macular degeneration. These cells do not detect light themselves; instead, they support the photoreceptors responsible for vision. Long-term follow-up showed that the transplanted cells could survive without major safety concerns, although clear improvements in vision remained difficult to establish.[8]

More recently, researchers have begun moving beyond the replacement of supporting cells towards replacing the neurons that detect light. In 2024, the US Food and Drug Administration cleared a first-in-human Phase 1/2a clinical trial of stem-cell-derived photoreceptor precursor cells for people with advanced retinitis pigmentosa.[9]

Getting cells into the eye is one challenge. Getting them to work is another.

Regenerative medicine has a difficult lesson to learn: a new cell is only useful if it becomes the right cell, in the right place, at the right time, connected to the right network.

In zebrafish, researchers have a biological model for how a damaged nervous system might rebuild itself. Their Müller glia demonstrate that cells with a supportive role can, under the right conditions, become a source of new neurons.

Scientists are now beginning to decipher those conditions.

For now, we have yet to switch on the regenerative potential of the human retina. But the idea that lost retinal neurons are beyond biological repair is no longer quite as absolute as it once seemed.

The zebrafish never forgot how to do this.

The question is whether some part of that regenerative programme can be recreated within us.

Perhaps the future of treating blindness will not depend solely on protecting the vision we have.

Perhaps, one day, we will learn how to grow it back.

References

1. Salman A, McClements ME, MacLaren RE. Insights on the regeneration potential of Müller glia in the mammalian retina. Cells. 2021;10(8):1957.

2. Ranski AH, Kramer AC, Morgan GW, Perez JL, Thummel R. Characterization of retinal regeneration in adult zebrafish following multiple rounds of phototoxic lesion. PeerJ. 2018;6:e5646.

3. Martins RR, Zamzam M, Tracey-White D, Moosajee M, Thummel R, Henriques CM, MacDonald RB. Müller Glia maintain their regenerative potential despite degeneration in the aged zebrafish retina. Aging Cell. 2022;21(4):e13597.

4. Todd L, Reh TA. Comparative biology of vertebrate retinal regeneration: restoration of vision through cellular reprogramming. Cold Spring Harb Perspect Biol. 2022;14(11):a040816.

5. Jorstad NL, Wilken MS, Grimes WN, et al. Stimulation of functional neuronal regeneration from Müller glia in adult mice. Nature. 2017;548(7665):103-107.

6. Wohlschlegel J, Finkbeiner C, Hoffer D, et al. ASCL1 induces neurogenesis in human Müller glia. Stem Cell Reports. 2023;18(12):2400-2417.

7. Todd L, Hooper MJ, Haugan AK, et al. Efficient stimulation of retinal regeneration from Müller glia in adult mice using combinations of proneural bHLH transcription factors. Cell Rep. 2021;37(3):109857.

8. Schwartz SD, Regillo CD, Lam BL, et al. Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies. Lancet. 2015;385(9967):509-516.

9. Gamm DM. Taking steps to restore vision: launching a stem cell clinical trial for retinitis pigmentosa. McPherson Eye Research Institute InSights. Fall 2024.