

Development of adult Stem cell based therapies for Glaucoma

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Glaucoma is a major cause of visual disability characterized by retinal ganglion cell (RGC) loss and damage to the optic nerve. Although current therapies can control disease progression, there is not available treatment for patients with late stage or aggressive disease. Blindness caused by glaucoma accounts for approximately 10% of the registered blindness every year in England and Wales, whilst globally there are 7 million people blind as a result of glaucoma. Visual loss due to glaucoma is irreversible and blindness occurring with rapidly progressive disease may only be prevented by cell replacement before total vision loss occurs. There is evidence that only a small number of retinal ganglion cells are needed to maintain visual function, for which transplantation of these cells into patients with late stages of disease could potentially maintain vision and improve their quality of life.

A considerable proportion of patients with advanced glaucoma, despite having lost more than 90% of their RGC layer, still maintain enough central vision to remain independent and maintain a reasonable quality of life. This suggests that less than 10% of nerve fibres are sufficient to maintain functional central vision, and that perhaps only a small number of RGCs might enable processing of visual signals that make the difference between preserved central vision in advanced glaucoma and blindness. If just a small percentage of RGCs could be functionally maintained by protective factors released by stem cells, or transplanted RGCs could be made to establish synapses with the limited number of existing RGCs in the patient's retina, it may be possible to maintain a minimal small amount of central vision without the need to form new axons and regenerate the optic nerve. Maintaining those few surviving RGCs during latter stages of glaucoma may therefore prove invaluable in maintaining the quality of life for such patients.

Our research therefore aims to optimize stem cell therapies to prevent progression or improve RGC function in patients affected by late stages of glaucoma. The work involves the co-operation of non-clinical interdisciplinary scientists and specialist clinical investigators based at the UCL Institute of Ophthalmology at Moorfields Eye Hospital.



Team photograph Courtesy of Vin Kumar, Medical Research Council

The retina

The retina is the sensory part of the eye that transmits light signals to the brain and allows us to see. It contains six types of nerve cells that send cascade signals onto each other and into the brain via the optic nerve (Fig 1). In many retinal degenerative diseases, damage to specific neurons or their supporting cells (retinal pigmented epithelium- RPE), leads to widespread neural cell death. Whether neural cell death is due to genetic defects, injury or chronic disease, the ultimate reason for blindness due to retinal disease is neural cell death.

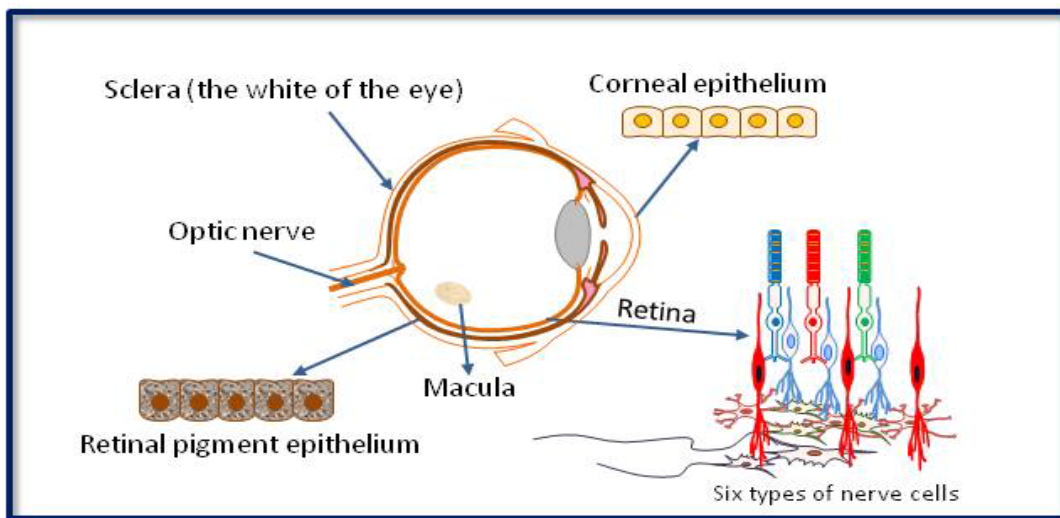


Fig 1. Schematic representation of the eye and the major cell types present within its different compartments

Investigations into the application of Müller stem cells to glaucoma therapies

The adult human eye harbours a population of glial cells (from the Greek word meaning 'glue'). A small proportion of these cells have stem cell characteristics and are known as Müller stem cells. Within the retina, these cells can be identified by their staining for specific markers of glial cells such as Vimentin, and markers of neural stem cells during early development, such as Nestin and Sox2 (Fig. 2).

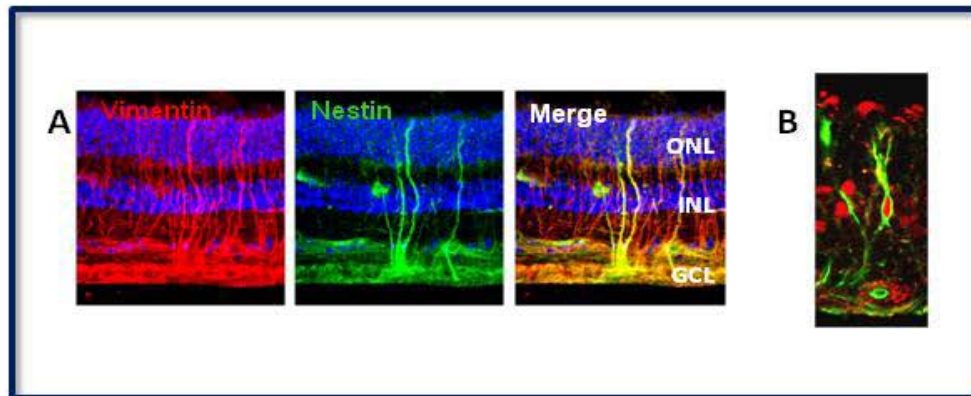


Fig. 2. The adult human retina contains a population of glial cells (from the Greek word meaning glue'), known as 'Müller glia'. A small proportion of these cells are Stem cells that can give rise to nerve cells in the laboratory.

This picture shows a microscopic image of human retina (the light sensitive part of the eye that contains nerve cells) illustrating the presence of Müller stem cells. (A) cells staining for the protein Vimentin (red), a marker of Müller cells, and Nestin (green), a marker of nerve stem cells. Cells that stain for both proteins (yellow) are the Müller glial cells with stem cell properties. (B) Müller stem cell within the adult human retina staining for Nestin (green) and Sox2 (red). These two proteins are present in stem cells during foetal development.

Müller stem cells can be grown in the laboratory and can be induced to become specific types of nerve cells (neurons). Newly differentiated neurons can be tested for their ability to restore visual function in animal models of retinal degeneration (Fig 3).

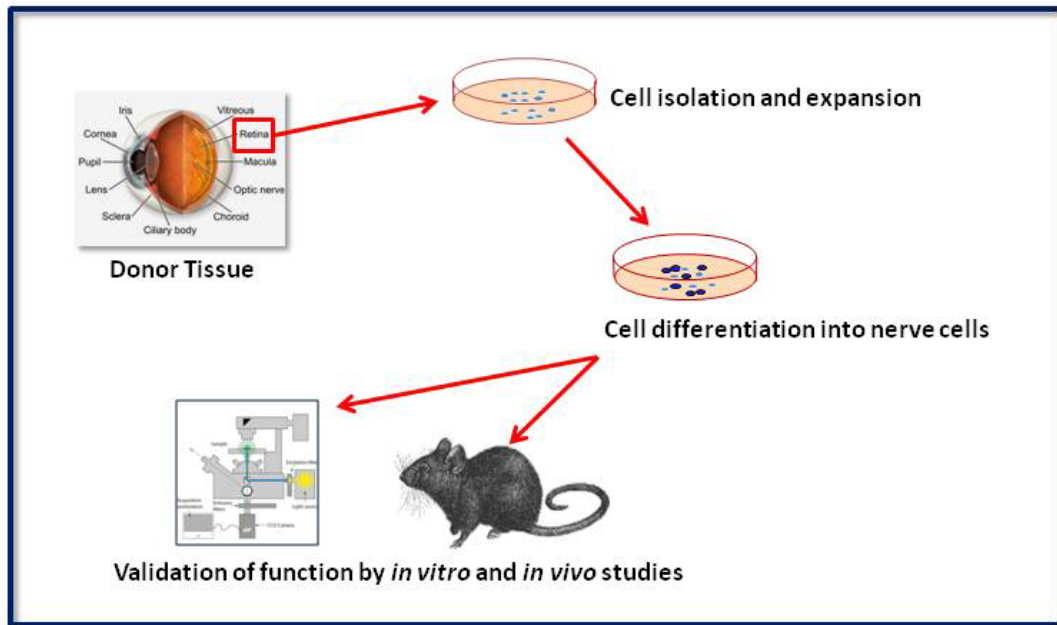


Fig 3. Müller stem cells can be isolated from adult donor retina and can be grown in the laboratory, where it can be induced to become specific types of retinal nerve cells (neurons). These neurons can be tested for their ability to restore visual function in animal models of retinal degeneration.

Müller stem cells can be cultured with various factors and induced to become retinal ganglion cells, the type of neurons primarily affected in glaucoma. Transplantation of these cells into the eye of rats with retinal ganglion cell damage (an experimental model of glaucoma-like damage) has shown to induce a partial restoration of visual function as measured by electrical responses to light (electro-retinography) (Fig. 4). Examination of retinal tissue from experimental animals transplanted with retinal ganglion cells show that these cells can attach to the retina and in some cases establish neural connections with other resident neurons (synapsis) (Fig 5).

In summary, our research aims to develop a stem cell therapy that can either delay loss of vision, and improve or partially restore retinal ganglion cell function in patients with late stage glaucoma at risk of becoming totally blind. This still requires the refinement of techniques for safe delivery into the eye, as well as the preparation of clinical grade cells that can be administered to patients under regulatory approvals.

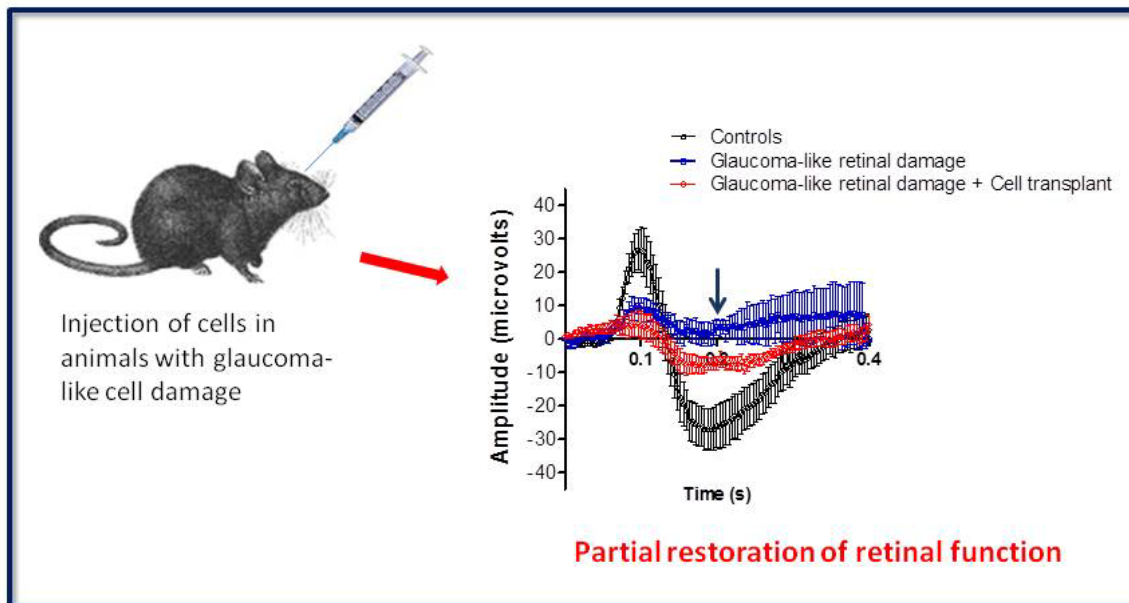


Fig 4. Measurement of retinal function in animals with glaucoma-like damage with and without transplantation of retinal ganglion cells by electrical responses to light (electro-retinography). The blue arrow indicates the response of retinal ganglion cells to very low light levels, with the black line indicating normal function, the blue line the depleted function, and the red line the partially restoration of function by cell transplantation.

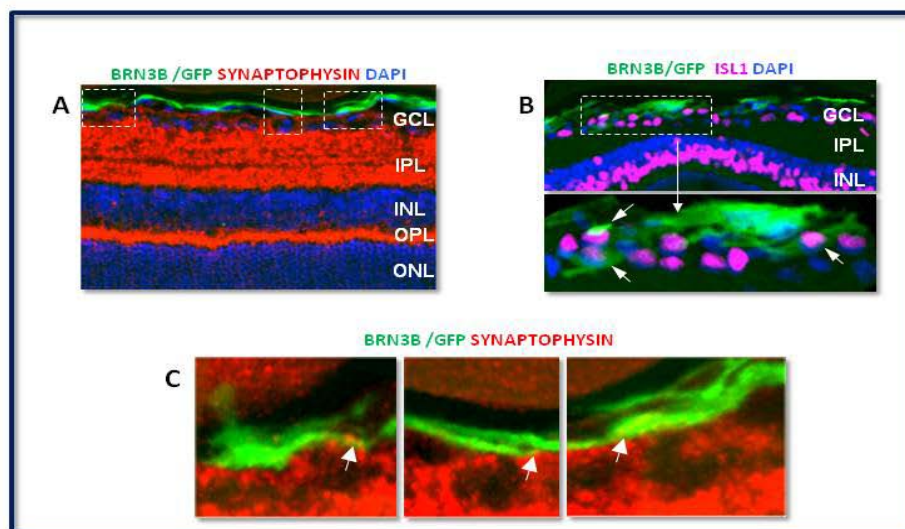


Fig 5. Microscopic images of rat retina transplanted with retinal ganglion cells (the nerve cells affected in glaucoma). (A) When retinal ganglion cells are transplanted into rat eyes with glaucoma-like damage, they attach and migrate into the retina (green cells). (B) Transplanted cells that migrate into the rat retina stain for the protein ISL1 (purple), which is present in retinal ganglion cells. (C) Transplanted cells align with the host cells and form nerve connections (synapses), as shown by staining for the synaptic protein synaptophysin (yellow), as indicated by arrows.

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