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MacularNEWS

We introduced our stem cell research in the previous MacularNEWS back in April 2015. Thanks to your generous donation and support, we have made progress with this project. In this edition of MacularNEWS, we would like to present the latest updates on our stem cell research and our future plans.

Generation of Retinal Müller Glial Cells from the Human Stem Cells: The World's First Attempt

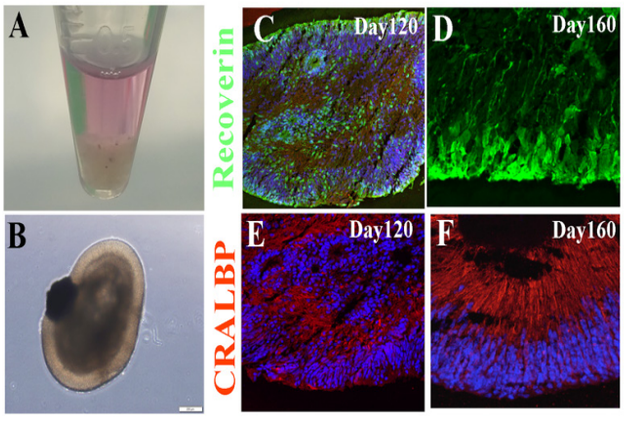
Apart from the blood vessels, there are basically two types of cells in the retina. The "neuronal" cells, or nerve cells, pick up and transmit the light, while the glial cells support them.
Müller cells are the major glial cells in the retina. Most research on regional disease concentrate on neuronal cells, but we believe that disease of glial cells is an important and overlooked cause of retinal disease. Glial cells are one of the most important sources of energy for photoreceptors, which are the neuronal cells that detect light.

We previously described in MacularNEWS how we can make patient specific stem cells for their own cells. Since then, we have been researching how to generate Müller cells from these human stem cells. Ultimately, we would like to try to treat some retinal diseases by transplanting healthy Müller stem cells, but so far no one has been able to differentiate Müller cells from human stem cells.

Here, we would like to present two ways that we have been trying to make Müller cells from human stem cells.

1. Organogenisis - Making 3 Dimensional Retinal Cups from Human Stem Cells

In 2014, a fascinating new method to make whole retinas from human stem cells was published in *Nature Communication.* It was possible to produce whole retinas with individual retinal cell types (the retina consists of 11 layers with 8 different cell types), even though they only lasted a couple of months before they fell apart. We have adopted the method in our lab, and here, we present our retinal cups derived from human stem cells after 120 and 160 days of culturing them in a test tube. Figure 1 shows our three dimensional retinal culture in a microtube (A), and a microscope image of the typical shape of a three dimensional retina (B). We have labelled the retinal cup with Recoverin, a marker for the retinal photoreceptors, and CRALBP, which is a Müller cell marker, confirming that we have produced both photoreceptors and Müller cells.



[Figure 1] Generation of three-dimensional retinal cups from human stem cells. 160 days after culturing the retinal cups, we found cells expressing the photoreceptor marker Recoverin and the Müller cell marker, CRALBP.

Our research relies exclusively on external grants and fundraising.

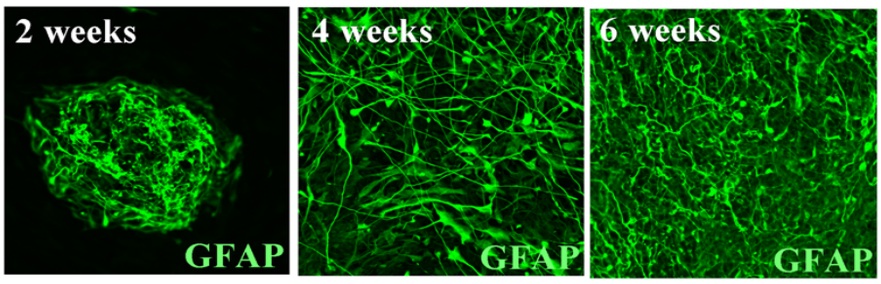
If you are in a position to support macular research, please know that we are extremely grateful and that your donation will be well used.

You may also like to consider remembering macular research in your will.

Thank you for your support.

Prof. Mark Gillies
Macula Research Group

To stay updated on all macular research and patient events please email macular.news@sydney.edu.au and ask to be placed on our e-mail notification list.



[Figure 2] Retinal stem cells expressing Müller cell marker, GFAP, after the promotion of the Notch signalling pathway.

2. Promotion of the Notch signalling pathway in retinal stem cells

Our second strategy to make Müller cells from stem cells is to modulate the Notch signalling pathway in retinal stem cells. The Notch signalling pathway is known to promote Müller cell formation when the retina is first developing in embryos. We made retina-specific stem cells first using an established method, then we treated the cells with two different proteins (DLL4 and Jagged-1) to activate the Notch signalling pathway in these cells. A few weeks after treatment, we found that the cells were expressing high levels of Müller cells with specific markers, such as glia fibrillary acidic protein (GFAP) compared with untreated cells. Figure 2 shows the retinal stem cells expressing GFAP two, four and six weeks after promoting the Notch signalling pathway.

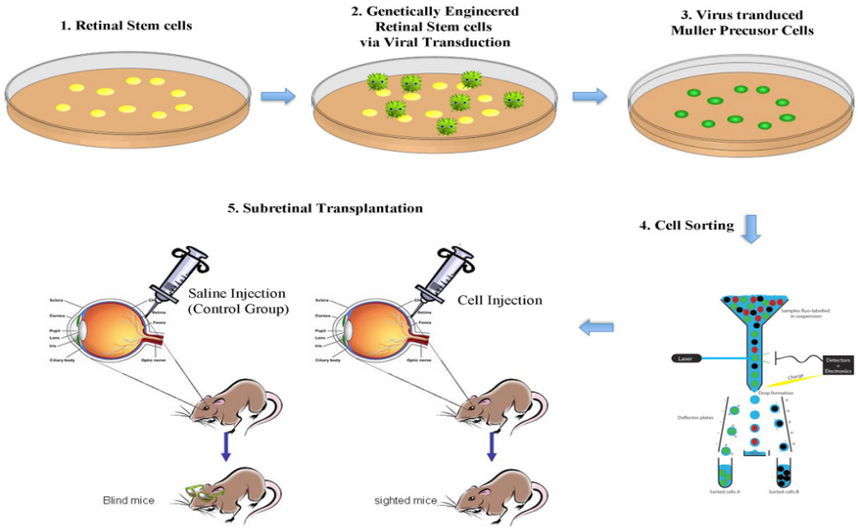
Future Research Strategy: Pre-Clinical studies are important for the development of new treatments

We now plan to conduct pre-clinical studies transplanting these cells into our mouse model (also previously described in MacularNEWS) in which we can "knock out" retinal Müller cells. These mice develop many features that are similar to some retinal diseases.

We are concerned that transplantation of mature Müller cells may cause complications and they may also be unable to migrate into the retina. Thus, we plan to use genetically engineered retinal stem cells, which will turn on the Notch signalling pathway and become Müller cells only after they have migrated to the retina. We expect to get better results this way with a reduced risk of unwanted side effects. We will study whether the transplantation will rescue the retinal degeneration and restore normal retinal function.

There are many barriers to retinal stem cell therapy. We expect that this will be a long road, but we won't know what the barriers are until we start the experiments. We plan to begin these transplantation experiments in our mice in the New Year.

Strategies for our pre-clinical study using stem cells. This study, using transgenic mice, will provide a foundation for the development of future treatments, such as cell replacement therapy.



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