Macular*NEWS*

Autumn 2012 4th Edition

http://sydney.edu.au/medicine/mac

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The Macular Research Group

Welcome to the 4th edition of Macular News.
In our last newsletter we described the "Fight Retinal Blindness!" project in which we have written a computer program to track across Australia the responses to treatment with the new drugs for wet macular degeneration.

In this newsletter we will describe how we set about trying to prevent blindness from a poorly understood macular disease that currently has no treatment.

The Laboratory Research Unit

undertakes studies in test tubes and animal models which are designed to understand and develop new treatments for macular disease. The group includes 3 scientists, 4 postgraduate students and a research assistant. In our first newsletter we described our laboratory research which aimed to develop stem cell treatments for advanced diabetic retinopathy. In our laboratory we are also trying to find treatments for a condition known as Macular Telangiectasia, or "MacTel".

Why we use animal models

We only use animal models when the studies we wish to perform cannot be done in test tubes. Our mice are treated humanely at all times and are anaesthetized for all procedures. They may have some reduction in visual responses, however because we only knockout patches of Muller cells they still seem to have reasonably normal visual function.

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Our Aim: *To develop new treatments that reduce blindness from macular disease, through multidisciplinary, patient oriented, world class research*

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MacTel

Is a condition in which the blood vessels of the macula become "telangiectatic", which means dilated and leaky. Varicose veins are a type of telangiectasis. It almost always affects both eyes and is often confused with Macular Degeneration even by Eye Doctors As well as the changes in blood vessels, people with MacTel begin to lose the cells that detect light, the photoreceptors, from their central maculas causing loss of vision. Fortunately MacTel progresses slowly, there are no treatments for it so it can cause loss of central vision.

Muller cells

are the main supporting cell of the retina and are closely related to both macular blood vessels and photoreceptors. It was thought that MacTel may be caused by a disease of Muller cells, however there was no direct proof of this. In fact nobody knows what diseases might be caused by defective Muller cells because they cannot be seen clinically. We were able to study the eyes of a MacTel patient who left their eyes to the project after they died, and found a loss of these cells from the central macula. This has not been described for any other disease. This is seen in the cross section of the macular from one of those eyes (see Figure 1) studied with a microscope. The Muller cells, which are stained red, are missing from the central macula but are normal at the edge of the retina.

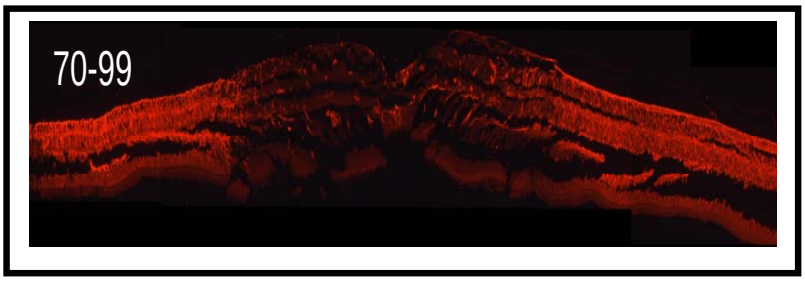

Figure 1: Muller cells

Based on this important finding, we set out to make an animal model in which we could remove or "Knock out" Muller cells to see whether it produced changes similar to those seen in MacTel. If it did, we could then see whether any drugs we had might be an effective treatment.

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A Mouse Model of MacTel

When we flicked the genetic switch in our "reporter" mice we confirmed that we were only destroying Muller cells by using a blue dye (see figure 2), which only showed in cells that spanned the full thickness of the retina and nowhere else. These results show that only Muller cells are being knocked out. Importantly, if knocking out Muller cells causes transgenic mice to mimic MacTel, we can be confident this is due to the destruction of Muller cells only.

When we knocked out Muller cells we were very pleased to find changes very similar to what we find in humans with MacTel. In microscopic studies to detect dying cells (marked as green dots in the figures 3 and 4) we found dying Muller cells in the inner retina within a day or two (See figure 3) followed by death of photoreceptors a few days after that (see figure 4). This suggests that death of Muller cells were causing death of photoreceptors, which is what we believe is happening in MacTel.

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"Transgenic" mice

Transgenic mice contain manipulated genes and have greatly expedited medical research. We have deployed this strategy as mice genes are similar to human genes and much simpler to work with. Our lab has generated a transgenic mouse that 'knocks out' Muller cells, with the goal of mimicking MacTel. This transgenic mouse may yield critical insight into what triggers MacTel and how the disease progresses. Importantly, this transgenic mouse will permit the testing of potential drug treatments for this blinding disease.

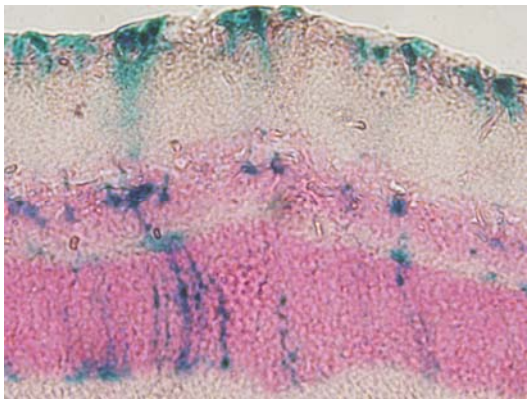
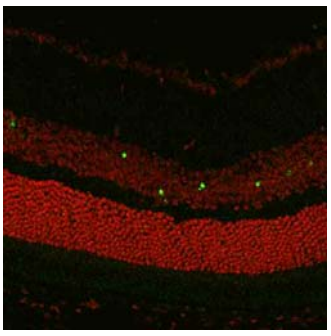
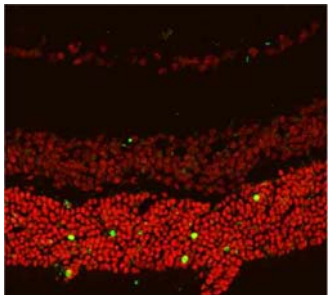


Figure 2



← Figure 3

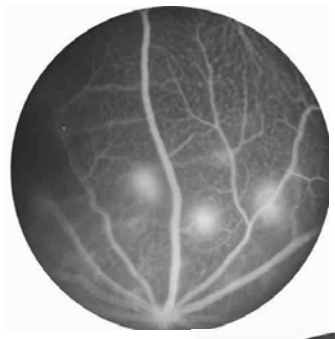
Figure 4 →



Where are we located?

You will find us at the Save Sight Institute, located at:
South Block, Sydney Hospital,
8 Macquarie Street, Sydney, NSW 2000

We also found changes in blood vessels in our mice which were similar to what we see in MacTel. These are shown in shown in the black and white macular angiograms (See Figure 5 and 6). The blood vessels are leaky in figure 5.



← Figure 5

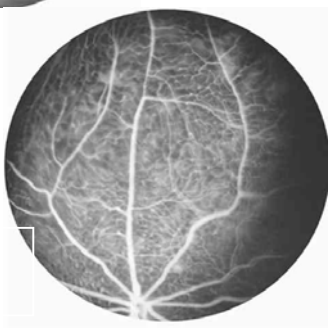


Figure 6→

Testing treatments for MacTel

We are now using this model to test for treatments for MacTel. The first effective treatment we identified was injections of steroids into the eye. We have used steroids in the past to treat diabetic retinopathy in humans. In the angiograms above the figure on the left is before treatment, the one on the right shows the same eye after treatment with steroid. The leak is dramatically reduced after treatment with steroid. We also found that steroid treatment reduced photoreceptor death. Another treatment that we have tested is a "neuroprotective" agent which was also effective in protecting photoreceptors. As a result the MacTel project has initiated the first clinical trial for MacTel in humans using this neuroprotective agent.

What's Next?

We will now use this model to explore how Muller cell dysfunction contributes to other retinal diseases, such as diabetic retinopathy, macular degeneration, retinal vein occlusion and retinitis pigmentosa. We hope that this research may identify new ways to treat macular disease.

To make a donation to support the Macular research team at the Save Sight Institute and the Sydney Eye Hospital, you may send a cheque to Professor Gillies made out to the "Macular Research Group" at the address below. No amount is too small or too large. Any excess funds will be used to establish a scholarship for future PhD students of which we start around one every year. Alternatively you may complete the enclosed donation form.

You have received this newsletter because you have, or you have shown interest in, macular disease. If you would like to subscribe or do not want to receive this newsletter, just let us know on
02 9382 7309