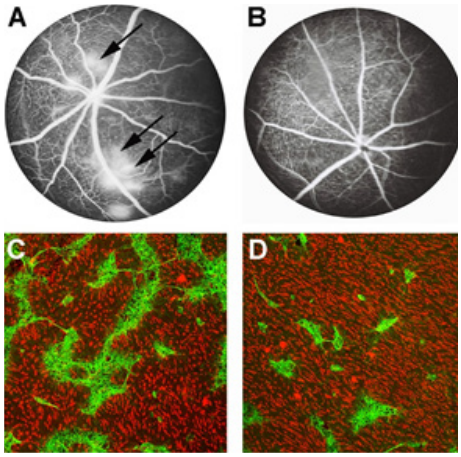
MacularNEWS

Autumn 2018 : Edition 16

Identifying New Combination Treatments for "Wet" AMD

Retinal fibrosis (scarring) that accompanies the growth of abnormal blood vessels in "wet" age-related macular degeneration (AMD) is one of the commonest ways to lose vision irreversibly, even in eyes that are receiving an adequate number injections. The laboratory unit of the Macula Research Group has generated genetically engineered mice which develop features simular to wet AMD. They are currently collaborating with a pharmaceutical company to identify new treatments to prevent the scarring that can happen in wet AMD. They are optimistic that they can identify a combination drug therapy which can prevent bleeding and leaking from the invading vessels and prevent the formation of retinal scars at the same time (see Figures below).



(A and C): genetically engineered mice develop blood vessel leak (A, arrows) and retinal scarring (C, stained in green). (B and D): a new combination therapy effectively inhibited retinal vessel leak (B) and reduced the formation of retinal scar tissue (D).

Director's Message

In this edition, I am pleased to provide a snapshot of our current research on how different types of cells in the retina cause blinding retinal diseases.

I am also excited to share about the expansion into Europe of our Fight Retinal Blindness software that tracks the outcomes of treatment of retinal disease.

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.

Thank you for your support.

Prof. Mark Gillies
Macula Research Group

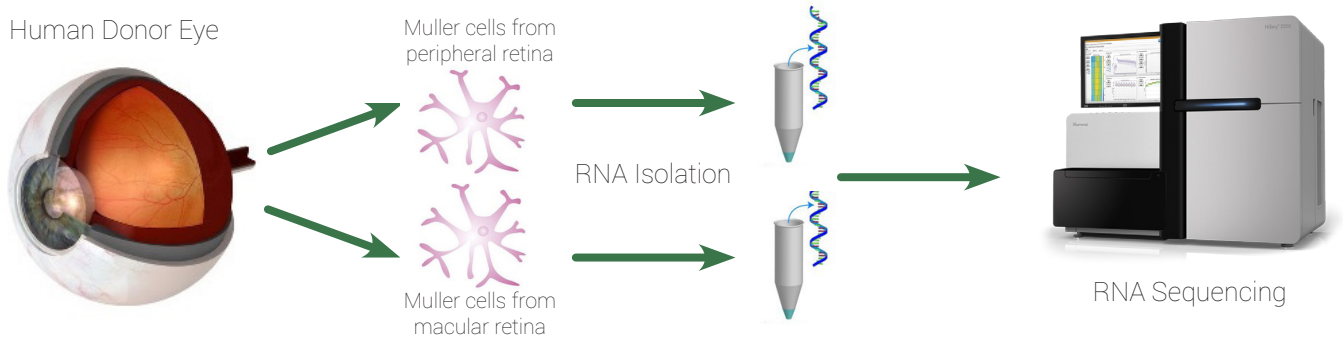
To stay updated on all macular research and patient events please email macular.news@sydney.edu.au and ask to be placed on our e-mail notification list.

"Why is the macular so susceptible to disease?"

It remains a mystery why some retinal diseases, such as age related macular degeneration or diabetic retinopathy, only occur in the central (macular) region of the retina. We believe that this may be partly because the Müller cells, the major supporting cells of the retina which we have written about before because we are very interested in them, are different in the macula compared with the rest of the retina.

Our recent studies in our lab suggest that there may in fact be two types of Müller cells in the retina which have different functions. One type of Müller cells is mainly distributed in the macula and the other is primarily located in the peripheral retina. These 2 types of Müller cells may be different because the environment of the macula is different from the rest of the retina. We are on our way to identifying what is different about Müller cells from the macula because this may be the cause of diseases that only affect the macula. Understanding this in more detail might identify new targets for the treatment of macular diseases.

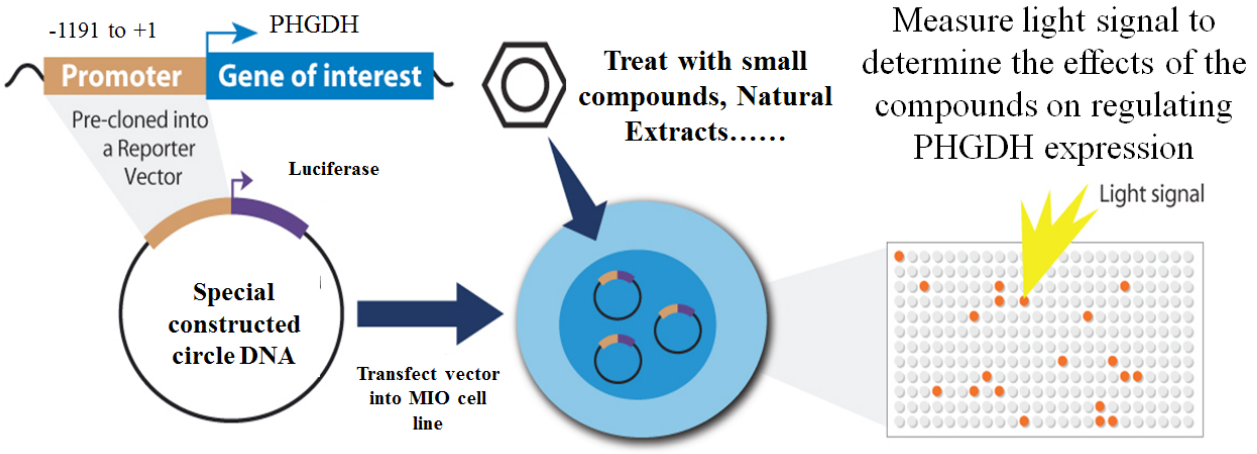
We isolated and cultured Müller cells in a test tube from human donor retinas to compare Müller cells from the macula and the rest of the retina. We extracted out of each group of Müller cells and analysed the properties of cellular messenger RNAs, which are the molecules that are used to transform the genetic code (DNA) into the proteins that the DNA encodes. We were excited to find that there were many significant differences in the messenger RNAs between Müller cells from macular and peripheral retinal regions. We are now testing our hypothesis that the macula is more susceptible to disease than the rest of the retina because of defects in the macula-specific functions of Müller cells.



How to analyse the difference of Müller cells between macular and peripheral retina.

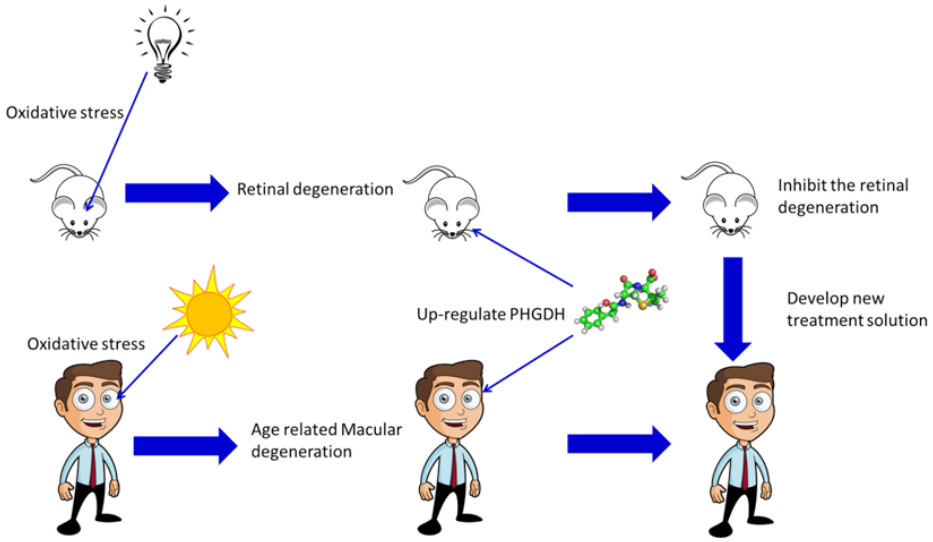
One of our findings was that the expression level of an enzyme called phosphoglycerate dehydrogenase (PHGDH) in the macular Müller cells was very different from those from the peripheral retina. I know that this sounds boring, and there was a time when I would have agreed with you, but now that we are researching retinal metabolism it turns out that these biochemical pathways are very interesting because they may underlie many retinal diseases. PHGDH is a key enzyme in a chemical reaction that occurs in the retina that produces antioxidants. The macula has high levels of oxidative stress because it has the highest energy requirement of any tissue in the body and it also has light shining on it all day. We believe that low levels of PHDGH may be a cause of macular disease. We have not published this yet so please don't tell anyone.

Now we are developing ways to boost PHGDH expression in macular Müller cells to fight oxidative stress as a new way of treating macular diseases. We have constructed a high-throughput drug screening system to select compounds that can boost PHGDH expression in Müller cells. We can screen tens of thousands of chemical or natural compounds in a short time with this system. We have developed a gene construct that links a protein that glows in the dark, "luciferase", with the "promoter" region of the PHDGH gene which turns the PHGDH gene on. Any potential drug we screen that boosts the PHDGH promoter will light up the well of the plate that that particular drug has been put into as shown in the diagram that follows.. We will then narrow down the drugs that we are screening for more advanced laboratory testing.



High-throughput drug screen system for compounds that can upregulate PHGDH production

We have found a natural compound, together with its bioactive analogue which has been modified to increase its activity, that efficiently upregulates the expression of PHGDH in Müller cells in both the cell culture experiments and studies of whole human retinas in a test tube. We are now testing these compounds in a mouse model of retinal degeneration that is caused by bright light. There is a long road ahead to bring these agents to clinical trials, but the Macula Research Group has both laboratory and clinical research units so we are confident that we can do this if the drugs we have identified continue to pass all the tests.



Validate candidate compound in retinal degeneration mice

Meet the Laboratory Team

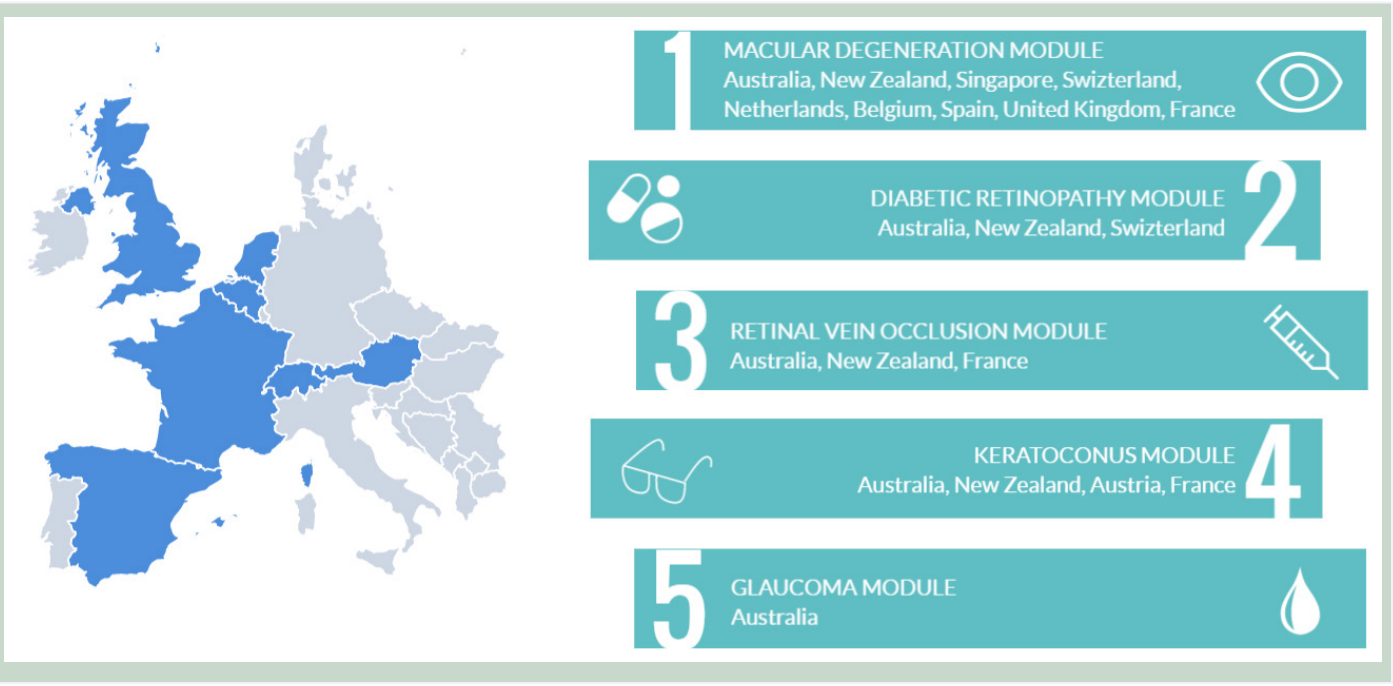
From left to right: Bobak Bahrami(PhD Student), Sora Lee (Research Assitant), Weiyong Shen (Senior Research Fellow), Mark Gillies (Director of Research), Ling Zhu (Postdoctoral Research Fellow), Ting Zhang(Visiting Scholar), Ashish Mathai (Research Assistant), Rui Zhang (PhD Student)

FRB! Project in Europe

Save Sight Registries (SSR) leads the way in providing researchers and clinicians around the world the means to measure patients' treatment outcomes efficiently, securely and in a standardized way. Our internet-based platform facilitates the collection, storage and analysis of quality data from routine clinical practice in Ophthalmology.

The Fight Retinal Blindness! Project has conducted over 20 analyses providing real world evidence of treatment trends for wet Age-related Macular Degeneration. Our strong collaborative research focus has resulted in encouraging interest and uptake of the FRB system in various countries around Europe.

We have completed a successful Pilot Project in the Netherlands where it has been given the thumbs up as the "best possible solution" as a quality registry for nAMD in the Netherlands. Over this time, we have enhanced our system to meet the European General Data Protection Regulations to facilitate the increasing European uptake of our registries into other countries. We are also currently preparing for the implementation of our system into four Eastern European Countries interested in real world evidence findings, through our Registries, to improve patient outcomes.



SSR have determined treatment patterns that are most effective for treating wet AMD. These findings have been published in leading international journals. It is expected that global uptake of the Save Sight Registries, will advance international scientific collaboration to improve patient outcomes globally.

If you would like to make a tax-deductible donation or discuss leaving a bequest to support macular research please visit our website http://www.savesightinstitute.org.au/single-gift, call us on (02) 9382 7309 or post a cheque to Save Sight Institute, South Block, Sydney Eye Hospital.

Save Sight Institute is a centre of The University of Sydney.

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