Macular Disease Foundation AUSTRALIA™

Our focus is your vision

Macular Degeneration Research Update December 2014

Macular Disease Foundation Australia strongly supports Australia's contribution to the enormous global research effort underway to better understand why macular degeneration develops and how it can be treated, and hopefully cured. This update provides a broad summary of some of the interesting and promising research programs that are being undertaken around the world. Unless otherwise stated, the treatments and products mentioned in this update are still not generally available.

How does macular degeneration develop?

Oxidative stress

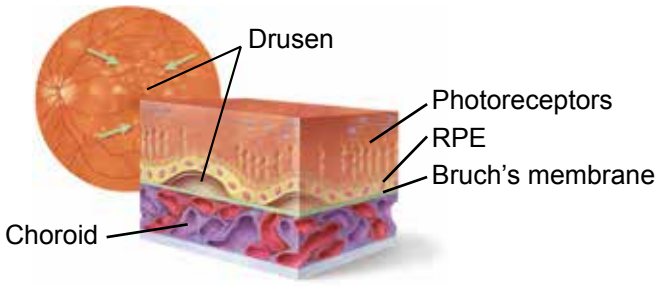
All cells obtain energy by combining the nutrients from digested food with oxygen from the bloodstream. This process produces toxic waste products called free radicals, which can cause "oxidative damage" to the cells. This can be thought of as a type of rust. Eating a healthy diet rich in anti-oxidants normally results in the removal of free radicals and repair of most of the damage that has occurred. If the diet is low in anti-oxidants, or if additional toxins are added, such as from smoking, the cells may be unable to cope and can suffer from 'oxidative stress', leading to cell damage.

Reducing inflammation

When cells are damaged, the normal repair process involves inflammation. This is a complex process and includes increased blood flow to the tissues. New blood vessels may form, and the vessels can become leaky, leading to swelling. Although inflammation is a normal part of the body's repair mechanism, if prolonged or over-stimulated, it can cause many problems.

How does this relate to age-related macular degeneration (AMD)?

In people with AMD, a combination of oxidative stress and inflammation are important factors causing damage or death to certain cells in the retina, the light sensitive tissue at the back of the eye. Waste products inside the retina are normally removed via a layer of cells called the **retinal pigment epithelium (RPE)**, which lies directly under the photoreceptor cells which convert light signals into messages to the brain.



If waste products are not cleared away, they can form deposits called drusen. Drusen are a sign of **early macular degeneration.** There is normally little or no loss of vision with early AMD. About 12% of Australians over 50 (962,000 people) show evidence of early macular degeneration which can be diagnosed during an eye check.

Drusen appear to impede the delivery of nutrients and oxygen to RPE cells and the photoreceptor cells. In some people, these changes gradually cause the death of RPE cells and then the photoreceptors, producing 'worn out' patches (atrophy) and loss of central vision. This is called **dry macular degeneration** and the late stage is called **geographic atrophy.** About 71,000 Australians have late stage dry macular degeneration, for which there is currently no treatment.

One of the responses to the lack of oxygen can be the increased production of several proteins which stimulate the growth of new blood vessels. One of these growth factors is **vascular endothelial growth factor** or **VEGF**. In some people, the new vessels grow out of control and they start to leak fluid and/or blood under the retina. This can cause rapid changes to the structure and function of the retina. If untreated, it quickly leads to RPE and photoreceptor death with significant vision loss. This is called wet macular degeneration. About 122,000 Australians have wet MD for which there is effective treatment available using anti-VEGF drugs.

What is the influence of genes?

Unlike some conditions which can be caused by a problem in a single gene, AMD is influenced by subtle variations in at least 34 genes. More genes are progressively being identified. These changes can increase or decrease one's risk of developing disease. An individual will have a mixture of "good" and "bad" genes, and scientists are still clarifying the relative importance of these.

What are clinical trials and why are they important?

Clinical trials are studies in humans which aim to find a better way to manage a particular disease. They aim to establish: correct dosage, safety, efficacy (how well it works), interactions with other drugs, comparisons to other treatments, cost effectiveness and use in specific medical situations. Trials are designed in a way that minimise the possibility of bias or incorrect conclusions.

Medical research phases

Research phase	Patients studied	What studied	Average duration
Discovery and development	Usually laboratory work	What causes the disease, identify targets (e.g. find a 'key' that turns off an unwanted process)	Many years
Pre-clinical	Animals or cell cultures	Proof of principle, safety in animals, safe starting dose, toxicity	4 years
Phase 1	20 to 80 healthy volunteers	Safety and dosing	1 to 2 years
Phase 2	100 to 300 volunteers with disease	Initial efficacy, dosing, larger scale safety	2 years
Phase 3	500 to 3000 volunteers with disease	Detailed efficacy, safety, comparison to other treatments	3 years
Registration and reimbursement		Regulators review studies and detailed manufacturing dossier to decide if treatment should be registered and subsidised	18-24 months
Phase 4	Consenting patients using the test treatment once launched	Long term safety and efficacy	Ongoing

How are drugs approved for use in Australia for safety and efficacy?

Once a manufacturer has completed the pre-clinical and phase 1 to 3 clinical studies for a new treatment, the Therapeutic Goods Administration (TGA) reviews vast amounts of data on how the research was conducted, and its findings. The TGA also reviews information about the manufacturing process to ensure that drugs are manufactured to specification. Only after the TGA is satisfied that the treatment has an acceptable safety profile and is effective, can it be registered for use in Australia.

What happens to make drugs affordable in Australia?

Following registration, the Pharmaceutical Benefits Advisory Committee (PBAC) reviews additional data regarding the safety, efficacy (effectiveness) and cost-effectiveness of a new treatment to decide whether it should receive a government subsidy and be placed onto the Pharmaceutical Benefits Scheme (PBS). Once a treatment is placed on the PBS, the patient will only pay a part of the actual cost of the drug, with the rest being subsidised by the taxpayer.

Research highlights 2014

Prevention – physical activity

A large study in Denmark involving 888 people recently showed that people who undertook 4 to 7 hours per week of moderate physical activity (walking, cycling, gardening etc) were 42% less likely to develop drusen larger than 63 microns in diameter (a precursor to macular degeneration) compared to people who did between 0 and 2 hours per week.

People who were able to do between 7 and 12 hours of physical activity per week were 67% less likely to develop drusen. Those who had a genetic predisposition to macular degeneration also benefited from maintaining an active lifestyle. In contrast, people with poor blood lipid levels (low HDL and high triglycerides) and a larger waist circumference were much more likely to have significant numbers of drusen.

Note: Always talk to your GP before undertaking a new or increased exercise program.

Early detection

AMD significantly slows the ability to adapt to seeing in dimly lit environments. Using this knowledge, researchers at Penn State College of Medicine have developed a very quick diagnostic test, taking less than seven minutes, to assess one's ability to adapt to the dark. Previous tests have taken over 30 minutes, making them impractical. This test was very accurate in detecting people with early AMD.

Treatments for early and dry AMD

Why is it taking so long for effective treatments to be developed for early and dry AMD?

1. AMD is a very complex disease. Development of AMD is influenced by age, environmental and genetic factors, and also involves the immune system which is one of the most complex systems in our body.
2. Early and dry AMD normally develop over many years or decades so it can take a long time to determine if a new treatment is actually having any effect on the disease.
3. The genetics of AMD is extremely complex.
4. There is no reliable "test-tube" or animal model of early or dry AMD to test new theories or treatments before they can be tested in humans and most animals don't have a macula. Many theories and treatments have appeared to be successful in mice or rabbits, but have been unsuccessful when tried in humans.

However, even with these ongoing challenges, great progress has been made in the last decade.

LXR Agonist

As a normal part of the function of the eye, fatty wastes are deposited under the retina. In young, healthy people, cells called macrophages “eat” and remove these deposits. As we age, macrophages become less efficient and inflamed, leading to a build up of waste (drusen) and in some people, the formation of unwanted new blood vessels.

An animal study has shown that macrophages can be rejuvenated with a drug called an LXR agonist, reducing the drusen that lead to dry macular degeneration and potentially preventing the formation of new unwanted blood vessels (wet AMD). This work now needs to be replicated in humans.

2RT laser

Previous research demonstrated that an ultra-short duration (“nano-second”) laser, developed in Australia, could safely remove drusen. Unlike other forms of laser, this laser does not appear to cause any damage to photoreceptor cells. A world-first, randomised trial of 240 patients is continuing at five centres in Australia and one in the UK to see if removing drusen with this laser in people with high risk early AMD is able to slow or halt the progression of disease. The trial has now been running for two years and over 200 people have now been enrolled. Half of the patients receive the laser treatment and half receive a placebo treatment. It is expected that the trial will be completed in 2018.

Emixustat (ACU-4429)

In May 2013, a phase 2 study showed that this drug, taken as a tablet, successfully slowed down the activity of rod photoreceptor cells. Rods are mainly used for night vision, and are very fragile, creating large amounts of waste that can build up in drusen. By slowing down rod function, waste production appears to be reduced, although a side effect is that the ability to quickly adapt to darker conditions is reduced. A phase 2b/3 trial began in 2013 to determine if reducing rod function reduces the generation of waste and slows the progression of dry MD.

This study is now fully enrolled and is expected to be completed in mid 2016. The US FDA granted this drug “fast track” status, a process that facilitates development, and expedites the review of drugs that fill an unmet medical need for serious diseases.

Lampalizumab

One of the major contributors in the formation of dry MD is the malfunctioning of part of the immune system, known as complement. Complement helps or “complements” our antibody defence mechanism. Some people carry one or more genes causing overactivity of the complement system, leading to inflammation and progression of AMD.

Lampalizumab is the first drug that has been shown to provide a benefit for people with late stage dry AMD. A large phase 2 trial known as MAHALO, showed that this treatment, given as an eye injection every month to people with advanced dry AMD (geographic atrophy), produced a 20% reduction in progression of the scarred area at 18 months.

In a subset of people with a reasonably common gene, a 54% reduction in progression was seen.

In 2014, it was announced that two large phase 3 trials have started in order to confirm safety and efficacy, and hopefully enable registration. These studies are being conducted in people with end stage dry AMD only (geographic atrophy) with no history of wet AMD.

Treatments for wet AMD

Current anti-VEGF treatments

Over the last seven years, anti-VEGF injections have become standard treatment for wet AMD. A very large analysis of the outcomes in the UK using existing anti-VEGF injections reinforces the importance of starting treatment for wet AMD as soon as leakage or bleeding occurs. The study

found that people who start treatment early, when their vision is still good, will typically maintain good vision, even though it may not necessarily improve. In contrast, people who start treatment late, when vision has already deteriorated significantly, may notice some improvement in vision, however vision will generally remain relatively poor.

If you have early (dry) AMD, it is important to monitor vision daily, one eye at a time, ideally with an Amsler grid, as the dry form can turn to wet. If you notice any sudden changes in vision, it is critical to see your optometrist or ophthalmologist immediately in case new leakage has occurred, necessitating early treatment. Without treatment, wet AMD will almost always result in significant and permanent vision loss.

Anti-VEGF drugs by eye drops

Anti-VEGF drugs that are currently used to treat wet AMD must be administered by regular injections into the eye. Research at the University College London has shown that in animals, it is possible to use tiny nano-particles which contain an anti-VEGF drug that can be delivered by a daily eye drop. Previous attempts at an anti-VEGF eye drop have failed to deliver adequate levels of the drug to the retina at the back of the eye. Further research is now needed to see if the drops work as well in humans.

Squalamine

The development of an eye drop to treat AMD has been a key focus of research. The results of a phase 2 study in June 2014 on the use of squalamine eye drops in humans with wet AMD takes this a step closer to reality.

At the start of the study, all patients received an injection of the anti-VEGF drug, Lucentis. Half the patients then received squalamine eye drops, given twice per day, while the other half received placebo eye drops (drops that appeared the same but did not contain squalamine). All patients also received additional injections of Lucentis as needed. Patients were followed for nine months.

Although the use of squalamine drops did not reduce the number of injections required, the people receiving squalamine showed much better improvement in vision. The number of people who could read three or more lines on the eye chart increased from 21% in the Lucentis + placebo group, to 48% of people in the group which received both Lucentis plus squalamine. The results were even more impressive in people with a certain type of lesion called “classic”.

Two large phase 3 trials (needed for registration) will commence in early 2015, in which patients will be treated for nine months.

Fovista

This drug is given in combination with existing anti-VEGF injections. It blocks another growth factor called PDGF, making leaky new blood vessels more susceptible to the effects of anti-VEGF drugs. In a phase 2 study, this combination with anti-VEGF injections resulted in the ability to read an additional 6.5 letters (more than one line) on the eye chart, in people who had already been treated with an anti-VEGF on its own. Fovista was well tolerated. Three large phase 3 (registration) studies are now recruiting patients and are planned to be completed in 2016.

X-ray treatment

A treatment involving the use of a low energy, highly targeted X-ray to the macula, in patients who are receiving anti-VEGF injections is now approved and in limited use in Europe. The treatment (called IRay),is intended to be given as a one-time therapy, in the hope of reducing the number of anti-VEGF injections. It resulted in a modest average reduction of about one injection in each of the first and second years. Results were somewhat better in a subgroup of people with certain characteristics.

One of the concerns about X-ray treatment is the potential for a serious complication called radiation retinopathy. In September

2014, a 3-year safety follow-up was published indicating that while 12% of people experienced some radiation changes to the small blood vessels in the eye, these were generally very small and diminished over time. This treatment has recently become available at a few centres in the United Kingdom, Switzerland and Germany but is not yet available in Australia.

Gene therapy

In 2014, after 25 years of laboratory work, researchers in Perth released the preliminary results of a phase 1 trial of a new gene therapy for people with wet AMD, and potentially other diseases.

Patients with wet AMD who had previously needed regular injections of an anti-VEGF drug were given the gene therapy as a single injection under the retina. This injection contained a totally safe virus which had been modified to deliver a “therapeutic gene”. The gene instructs the eye to continually produce a naturally occurring protein called sFLT-1, which acts in a similar way to anti-VEGF drugs.

It takes six to eight weeks for the eye to produce adequate quantities of the protein, so all patients also received injections of the anti-VEGF drug, Lucentis, at the start of the study. After this, additional injections of Lucentis were only given if leakage of blood or fluid was not controlled.

Nearly all patients who received the gene treatment experienced good control of their wet AMD with improved visual acuity. Most required no additional injections of Lucentis over a 12 month period. Larger randomised trials are now underway in the USA.

The Foundation respects different points of view concerning stem cell research. The Foundation’s role is simply to report on key research for your information.

Stem cell treatment

Stem cells are special types of cells that can be transformed into other types of cell. The new cells can then be transplanted (into the eye for example) to replace damaged or dead cells. Some important progress in stem cell treatment was made in 2014.

Sources of stem cells:

1. Human embryonic stem cells (hESCs)

One or two cells are removed from an embryo. These cells are then cultured in the laboratory to produce many millions of stem cells which can then be coaxed into becoming the desired cell type. hESCs are the most adaptable type of stem cell as they can be converted into almost any type of cell.

2. Adult stem cells

These are usually obtained from either umbilical cord blood, or from bone marrow. These cells are more limited in the types of other cells they can produce.

3. Induced pluripotent stem cell (iPSC)

Certain types of adult cells such as skin or retinal cells can be re-programmed to revert back to being a type of stem cell, although they are more limited as to the type of new cell that can be formed.

Initially, stem cells are being used to produce new RPE cells which can be implanted into the eye. In the healthy eye, RPE cells lie under the photoreceptor cells, providing them with nutrition and removing waste products. In AMD, RPE cells become unhealthy or die which then leads to the loss of central photoreceptor cells and hence central vision.

The first human studies in this area are primarily to confirm the safety of implanted RPE cells. Initial studies are in a small number of people with very poor vision.

The ultimate aim of RPE cell replacement is for the procedure to be performed in people with earlier stage disease, so that the new RPE cells can prolong the function of existing photoreceptors. For those who have already lost significant vision, it is likely that their photoreceptors will have already died, and therefore, implantation of both RPE and photoreceptor cells may be needed. The development of photoreceptors from stem cells is many years behind RPE cells, however good progress is being made.

Advanced Cell Technology study

In October 2014, results were published for the first 18 people who received transplanted RPE cells derived from embryonic stem cells. Nine of the patients had late stage dry AMD and another nine had Stargardt's disease which is a form of macular degeneration found in younger people.

All of the patients given these cells initially had very poor vision with significant central photoreceptor loss. The RPE cells were transplanted at the edge of the damaged central macula area where there were still some functional photoreceptors cells present. To date, no major safety issues have been identified. The cells are stable and have not changed to other cell types (such as cancer cells).

Ten of the 18 patients demonstrated some improvement in their vision with some improving enough to read two to three extra lines on an eye chart. Seven patients experienced no change or a slight improvement and only one showed a further drop in vision. Larger phase 2 studies are planned in the US and UK.

Riken study, Japan

In September 2014, Japanese doctors performed the first transplant of retinal tissue derived from "induced pluripotent stem cells". These are stem cells that can be created from a person's own tissue and therefore provide a perfect genetic match. Because of this genetic match, the new cells should not be rejected by the body's immune system and there would be no need for anti-rejection drugs.

To generate the new tissue, a few skin cells were taken from the patient and coaxed into becoming stem cells. This technology was developed by the Nobel Prize laureate, Dr Shinya Yamanaka. These cells were then manipulated to become thin sheets of retinal tissue and then used to replace the patient's damaged tissue.

Many other stem cell projects are now underway at other centres.

Several more years work is required before any stem cell treatment is expected to gain registration and become readily available.

Please Note: There are companies promoting unproven and unregistered 'treatments' for AMD using products that are claimed to be stem cells. However, the fact is that there are currently no registered stem cell derived treatments for AMD available anywhere in the world. These promoted treatments are typically very expensive with little or no evidence of safety or efficacy in AMD. Some may be dangerous. The Foundation strongly advises all patients to talk with their eye specialist before committing to any unusual treatment.

Macular Disease Foundation Australia Research Grants Program

Research is a journey of discovery, with the ultimate destination being a place where we can save sight. Along the way we will learn a great deal that can yield major benefit.

The Foundation's grants and fellowships are a major contributor to Australian research in macular degeneration. They are awarded following rigorous evaluation, based largely on the National Health & Medical Research Council (NH&MRC) process, along with international peer review, to ensure that the successful applicants meet the highest standards.

The Macular Disease Foundation Australia Research Grants Program was launched by the former Governor General, Her Excellency the Honourable Quentin Bryce AC CVO, in 2011.

To date, over $1.5 million has been committed to Australian researchers to undertake exciting and critical research. Another round of grants is planned for 2015.

"Witnessing my father's sight deteriorate from macular degeneration was heartbreaking. I can only urge everyone to have their macula checked, and very importantly, urge our society to make a greater effort to find a cure for this disease, which unnecessarily disables many of our citizens."

Jan Utzon, Foundation Ambassador and son of Jørn Utzon, designer of the Sydney Opera House.

If you would like to donate to the Macular Disease Foundation Australia Research Grants Program call 1800 111 709 or donate online at www.mdfoundation.com.au

Please note: Research is a lengthy, expensive, high risk process. Many of the projects in this summary are still many years from completion and some will not make it through the rigorous development and clinical testing process. We have prepared this summary based on the information available to us at the time of publication, and it is not intended to describe all aspects of the relevant research. Circumstances are also likely to change. The Foundation does not accept liability for out of date, misinterpreted or incorrect information.

This summary does not constitute advice and you should discuss treatment options with your doctor. Discussion of a project does not constitute the Foundation's endorsement of that product or treatment, and should not be used for investment or treatment decisions. The Foundation is unable to recommend or facilitate the entry of any clients into a particular clinical trial as all trials have strict inclusion and exclusion criteria.

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November 2014