Macular Disease Foundation AUSTRALIA™

Our focus is your vision

Macular Degeneration Research Update December 2015

Macular Disease Foundation Australia is highly supportive of the significant global research effort that is devoted to better understanding how macular degeneration develops, and how it can be better diagnosed, managed, treated and eventually cured. This update provides a brief summary of some of the more 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

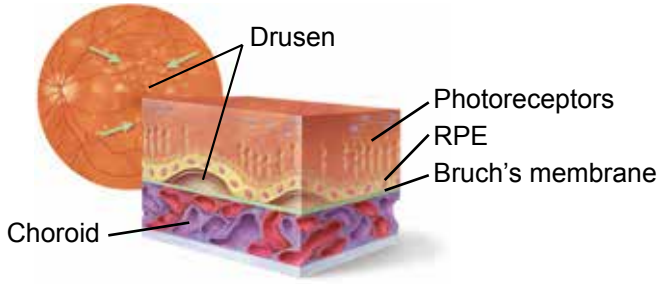
All cells obtain energy by combining the nutrients from digested food with oxygen from the bloodstream. This process produces toxic waste products called free radicals, which can cause "oxidative damage" to the cells. Eating a healthy diet rich in anti-oxidants normally results in the removal of free 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 a group of cells is 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 response 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 35 genes. More genes are being identified each year. 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.

Phases of medical research

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	1-2 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	Long term safety and efficacy	Ongoing

Accessing new drugs

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 TGA registration, the Pharmaceutical Benefits Advisory Committee (PBAC) undertakes a review (including cost-effectiveness) to decide whether a drug should receive a government subsidy and be placed onto the Pharmaceutical Benefits Scheme (PBS). Once a drug 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 government.

Research highlights 2015

Early detection

In research funded by the Foundation over the last 3 years, the Centre for Eye Research Australia has developed a number of breakthrough tests that can better predict at an early stage which people are more likely to develop the serious forms of disease. These tests are now under consideration for use as a better way to select the most appropriate people for clinical trials. This will reduce the number of people needed for trials, and also speed up the trials.

Disease formation

An important new area of research is the role of mitochondria. Mitochondria are tiny power stations inside cells that convert glucose into usable energy allowing cells to function properly. There is increasing evidence that problems in mitochondrial function may be an important factor in the development of AMD. Mitochondrial malfunction has already been implicated in several other diseases. Mitochondria can be damaged by such factors as cigarette smoke, toxic oxidised waste products from the diet and certain genetic conditions. Importantly, studies in cell cultures and in various animals have shown that certain compounds can protect mitochondria from this damage. Trials are now underway in humans to see if these compounds could be useful treatments for macular degeneration.

Research challenges

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

1. The development of early and dry AMD is extraordinarily complex, involving several body systems and numerous biological pathways. We may be able to block one pathway with a drug for example, but this is of little benefit if the disease then progresses down another pathway.
2. Dry AMD typically takes many years (or decades) to result in vision loss. It can therefore take a long time to determine if a new treatment is having any effect.
3. Unlike many diseases, we are not able to accurately mimic dry AMD in laboratory animals such as rats or mice as they do not have a macula and their eyes respond to treatments in different ways to humans.
4. Dry AMD is influenced by subtle variations in at least 35 genes, with additional relevant genes being identified each year. Testing treatments in people with certain genes (or combinations of genes) can produce very different results to people with other genes.

5. Early and dry AMD are significantly influenced by environmental factors such as diet, smoking and exercise. Since it is not practical for people in clinical trials to eat the same things for months or years, this means that the results from clinical trials of new drugs can be influenced by what people eat. This can make interpretation of results much more complex.

New treatments for early and dry AMD

2RT - laser

A world first, randomised trial called LEAD using an ultra-short duration ("nano-second") laser, developed in Australia, has recruited 292 participants from five centres in Australia and one in the UK. These people who have high risk, early stages of AMD will now be followed for a further 3 years to see if the laser is able to slow or halt the progression of disease. Unlike other forms of laser, 2RT does not appear to cause any damage to photoreceptor cells. The trial has already been running for three years, with half of the participants receiving 2RT laser treatment and half receiving inactive (placebo) treatment. The trial is expected to be completed in 2018.

Lampalizumab – eye injection

One of the main areas of dry AMD research is to reduce the inflammation that results from the malfunctioning of part of the immune system, known as complement. Complement helps or "complements" our normal antibody defence mechanism. Some people carry one or more genes causing overactivity of the complement system. If there is also damage to the retina due to factors such as smoking or oxidative stress from a poor diet, inflammation leads to tissue damage and loss of retinal cells, leading to geographic atrophy, the end stage of dry AMD.

Lampalizumab is the first drug that has been shown to provide a benefit for people with geographic atrophy. It does this by blocking a key enzyme involved in the complement system. A phase 2 trial called MAHALO showed that this treatment, given as an eye injection every month to people with geographic atrophy, produced 20% less growth of the scarred area at 18 months. In a subset of people with a reasonably common gene, 54% less scar growth was seen.

Two large phase 3 trials (CHROMA and SPECTRI) are now underway to confirm safety and efficacy, and hopefully enable registration. These studies are being conducted in people with end stage dry AMD only with no wet AMD. Injections will be given every 4 or 6 weeks and will be compared to a placebo. The studies are expected to be completed in November 2017.

Brimonidine for geographic atrophy – eye implant

Brimonidine is a drug that has been available for many years for the treatment of people with glaucoma. Animal studies have shown that when injected into the eye, brimonidine can protect nerve cells such as photoreceptors from the damaging effects of inflammation. It is now in a phase 2 study of 300 humans using a special slow release implant to minimise the number of injections needed. Results are expected in 2018.

Visual cycle modulation

One of the main contributors to inflammation is the build-up of toxic waste products under the retina. A drug called emixustat, given as a tablet, can reduce the amount of these waste products by slowing down the function of rod photoreceptors which are involved in night vision. Although a side effect of the drug was a slowing down of the ability to adapt to dark conditions, this was generally tolerable. A large phase 2/3 study in 480 patients is now underway to determine if the reduction in waste products slows the development of geographic atrophy. Results are expected in July 2016.

Macuclear – eye drop

In the normal eye, a layer called Bruch's membrane separates RPE cells from the underlying blood supply (called the choroid). As we age, Bruch's membrane changes and develops holes or gaps, which can allow

new, leaky blood vessels to grow under and into the retina. Macuclear is a new version of an old drug that is being tested to see if it can reduce the progression of dry AMD by improving blood flow in the choroid and maintaining the structure of Bruch's membrane. Initial studies have shown that the drug can be given as an eye drop and that it is able to improve blood flow in the choroid. A phase 2/3 study is due to finish in 2016 to see if it can slow the progression of dry AMD and preserve Bruch's membrane.

Lucentis for dry AMD – eye injection

Currently, Lucentis is only used in people with wet AMD. A new trial called PREVENT started at the end of 2014 in which people with dry AMD are given a Lucentis eye injection once every three months, to see if it will stop or reduce the progression from dry to wet. Patients will be followed for two years. Results are expected by September 2017.

Treatment of wet AMD

Although anti-VEGF injections are highly effective in most people with wet AMD, they do carry an ongoing burden of treatment as they require frequent, ongoing injections. A significant amount of work is underway to improve these treatments, including:

1. Using new delivery devices to provide long-lasting release of the drug into the eye
2. Developing new drugs which have a longer duration of effect
3. Developing eye drops which can be self-administered
4. Developing new drugs which work on different pathways and produce a stronger result
5. Implanting certain genes in the retina which stimulate long-term production of natural therapeutic proteins.

Delivery devices

Various technologies are being tested to provide longer lasting release of drug into the eye. Examples include the use of drug-impregnated particles, gels, refillable slow-release reservoirs or micro-pumps attached to the inside of the eye or implantable tubes containing drug that is slowly released.

Neurotech has developed a novel implantable rod called 'Renexus', which contains RPE cells that have been genetically modified to produce a therapeutic protein which does the same job as an anti-VEGF drug. Another version produces a protein which may protect photoreceptor cells for people with dry AMD. The cells are stored in individual rods that contain a solution that supports cell survival, and a membrane that enables the outward controlled flow of the protein and the inward flow of oxygen and nutrients without causing an inflammatory response. Multiple rods can be combined to form a device that is surgically implanted into the eye through a small incision and secured to the inside wall of the eye. These devices could potentially provide up to 5 years of treatment with a single procedure. Human studies are now underway comparing these to conventional injections.

A slightly different approach by a company called Avalanche involves the insertion of a gene inside a harmless virus shell (or vector) which is then implanted under the RPE layer of the retina. This gene then instructs the retina to produce a naturally occurring protein called sFLT-1 which has an anti-VEGF action, similar to the drugs that are normally injected. In theory, the protein should be produced for many years from a single treatment. Results of a phase 2a trial in 32 patients were reported in June 2015 showing the technique is safe and can reduce the number of injections needed. Further improvements to the procedure and vector are needed, and a modified vector is also being developed which would only require a single injection into the eye, rather than a surgical procedure to implant the gene under the retina.

New drugs

Pharmaceutical companies Novartis and Alcon have developed a drug called brolucizumab (RTH-258) which is an antibody against VEGF that is much smaller than current drugs. Initial human trials have

shown that this agent may have better penetration into the retina and a longer duration of effect compared to existing drugs. A large phase 3 trial in 1600 people is now underway and due for completion in early 2018. The trial includes a group receiving injections every 12 weeks. A new implantable, refillable micro-pump is also being developed which will allow the drug to be slowly released over many months. The pump could also be programmed to give different quantities of drug at different times, depending on the person's response.

Another pharmaceutical company Allergan is testing a new drug called abicipar (DARPin) which can be used in tiny quantities and appears to have a longer duration of effect compared to existing treatments. This drug may be particularly well suited to delivery via a slow-release implant.

Combining drugs

Because wet AMD is such a complex disease with multiple pathways, it is likely that a combination of drugs will be able to provide better outcomes.

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 of 449 patients, Fovista plus Lucentis produced significantly better results than Lucentis on its own. There is also evidence that Fovista may reduce the permanent scarring that typically occurs with wet AMD. Three large phase 3 (registration) studies are now looking at the use of Fovista in combination with all of the currently available anti-VEGF agents. These studies should be completed in mid 2016. If successful, the manufacturer could then apply for registration.

Squalamine eye drops

The development of an eye drop to treat wet 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 takes this a step closer to reality. The study combined the use of Lucentis injections with squalamine drops. At the start of the study, all patients received an injection of the anti-VEFG 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 9 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. Two large phase 3 trials (needed for registration) are due to commence shortly, in which patients will be treated for 9 months.

Stem cell treatment

Stem cells are special types of cells that have the remarkable ability to change into other cell types. The new "differentiated" cells can be grown in the laboratory and then be transplanted into organs such as the eye to replace damaged or dead cells.

Sources of stem cells: Human embryonic stem cells (hESCs)

One or two cells are removed from an embryo produced from *in vitro* fertilisation. These cells are then cultured in the laboratory and can produce a virtually endless supply of stem cells which can 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.

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.

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.

Induced pluripotent stem cells (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.

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 loss. Initially, most stem cell research has been directed to the use of stem cells to produce new RPE cells which can then be implanted into the eye.

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 people 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 much more complex and their success will depend on the new photoreceptors being able to make viable connections with the nerves leading to the brain. This is much more challenging.

Several human trials using stem cells for AMD have now started in other countries, although none have started yet in Australia.

Ocata Therapeutics (previously Advanced Cell Technology)

In June 2015, the American company Ocata reported follow-up results from four phase 1 trials on the use of hESC-derived RPE cells in people with very poor vision from late stage dry AMD (geographic atrophy) or Stargardt's disease. 31 patients were included in these trials with some having four years of follow-up. None of the 31 patients experienced any safety issues relating to uncontrolled growth of the implanted cells, rejection or serious side effects. Almost all of the patients experienced improved or stable vision, although specific details were not announced. As a result of these initial results, Ocata has now enrolled their first patients into a phase 2 trial in people with late stage dry AMD and Stargardt's disease. Another trial in people with myopic macular degeneration is also due to start.

London Project to Cure Blindness

After ten years of laboratory work and planning, this group reported in September 2015 that the first patient with sudden vision loss from wet AMD had received RPE cells derived from hESCs, implanted as a sheet under the retina. The project is being coordinated by Moorfields Eye Hospital in London, one of the world's leading clinical research institutions in eye diseases. Ten patients will be enrolled initially and followed for 12 months to assess safety and stability of these cells.

Riken, Japan

In September 2014, doctors in Japan 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, meaning the new cells should not be rejected by the body's immune system. There should also be no need for anti-rejection drugs. In May 2015, Riken announced that they had successfully produced a three dimensional structure in a culture dish containing multiple layers of retinal cells, including rod and cone photoreceptors. They have also shown that the edge of the structure can grow, suggesting that when implanted into the eye, the photoreceptors may be able to connect with the existing nerve tissue, which is critical if these cells are to ultimately restore sight.

The future for stem cell treatment

Many other stem cell projects are now underway at other centres. Human trials have not yet commenced in Australia.

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

Please Note: There are currently no registered (approved) stem cell derived treatments for AMD available anywhere in the world. Despite this, there are companies selling expensive, unproven and unregistered "treatments" for AMD using products that are claimed to be stem cells. Promotion of these 'treatments' typically involves dubious testimonials but little or no real evidence of safety or efficacy in AMD. Some of these treatments may be dangerous. The Foundation strongly advises all patients to talk with their eye specialist before committing to any unusual treatment.

Macular degeneration in the media

There are regular reports in the media about important research breakthroughs in the field, however many of these reports can be inaccurate or misleading. The Foundation constantly reviews the global media and endeavours to provide factual, objective and current information on latest developments. If you need further information on a media story, please see the Foundation's website or call on 1800 111 709.

Macular Disease Foundation Australia Research Grants Program

The Foundation's Research Grants Program is a major contributor to Australian research into macular degeneration. To date over $2.8 million has been committed to leading Australian researchers to undertake exciting and critical research.

The most recent grant recipients were announced on World Sight Day, 8 October 2015, at a special event at Admiralty House in Sydney hosted by the Governor-General Sir Peter Cosgrove. A total of $1.3 million was awarded to the 2015 recipients. Further details of the grants are available on the Foundation's website.

The recipients of the 2015 research grants.

Pictured are (L to R) Dr Gerald Liew, Prof Mark Gillies, Prof Robyn Guymer (on behalf of A/Prof Chi Luu), Lady Cosgrove, Governor General Sir Peter Cosgrove, Dr Isabelle Jalbert, Dr Laura Downie, Prof Steven Krilis

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. The Foundation has prepared this summary based on information available 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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