

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 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.

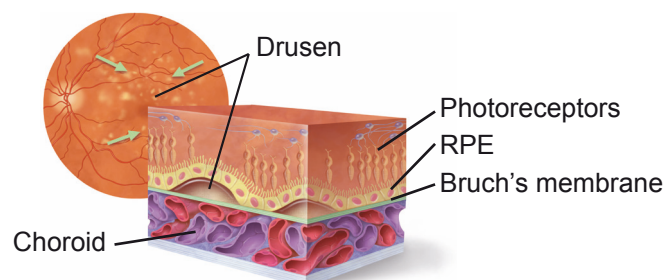
Inflammation

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 is 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 for safety and efficacy and then 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 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.

Research highlights 2016

Diet makes a difference!

A Portuguese study released in October 2016 demonstrated that a Mediterranean style diet, rich in fish, fruit and vegetables, nuts, whole grains and lean meats reduced the risk of developing macular degeneration by over a third. These results are very similar to those from a Foundation funded Australian study by Dr Liubov Robman (published in 2014) and are consistent with the Foundation's dietary recommendations. Contact the Foundation if you would like a factsheet on diet.

Potential treatments for early and dry AMD

2RT - laser

2RT is an ultra-short duration ("nano-second") laser developed in Australia that is currently being evaluated in a phase 3 trial in people with early stage AMD to see if the treatment reduces the likelihood of the disease progressing to the late stage.

Recruitment of patients for this study is now complete and patients are being closely followed to check for disease progression. 2RT has already been shown to reduce the number and volume of drusen under the macula, and does not appear to damage the retina, at least in the short term. It is not yet known however whether accelerating the removal of drusen has any effect on the progression of the disease. This will not be known until the final study results are released in 2018.

NOTE: Even though this is still an investigational treatment, the laser is available at some Australian clinics. Until its long-term safety and efficacy in early AMD are determined in 2018, the Foundation's Medical Committee recommends that the treatment should only be used inside a properly conducted clinical trial and, as trial participants, they should not be required to pay for the treatment.

Lampalizumab – eye injection

This drug is well into phase 3 trials in people with the late stage of dry AMD (or “geographic atrophy”). If these trials are successful, it could be submitted for registration, perhaps as early as 2019 and could then be available 18 to 24 months later. It would then be the first drug treatment available for late stage dry AMD.

This drug is given as an eye injection every 4 or possibly 6 weeks, and blocks a key enzyme in the ‘complement’ immune system which is believed to trigger the development of geographic atrophy. An earlier trial called MAHALO showed that this treatment produced 20% less growth of the damaged area of the macula after 18 months. In a subset of people with a reasonably common gene, 44% less growth of the damaged area was seen.

Two large phase 3 trials (called CHROMA and SPECTRI) are now underway to confirm safety and efficacy, and hopefully enable registration. These studies include sites in Australia.

High dose statins

Statins are oral drugs that are commonly used to lower blood cholesterol. The drusen that form under the macula with dry AMD are somewhat similar to cholesterol and several studies have been conducted to see if statins could also slow or stop drusen growth. All previous studies using normal doses have shown little or no benefit. A study released in 2016 using a much higher dose suggests that statins may possibly reduce drusen and improve visual acuity. A new larger study is now planned to confirm this finding.

Doxycycline (Oracea)

This is a drug that has been used for decades as an oral antibiotic, and it also appears to reduce the loss of photoreceptors. It is being tested in nearly 300 people with dry AMD with results expected at the end of 2018.

Photobiomodulation for dry AMD

The results of the TORPA II study suggest that people who receive a treatment involving certain wavelengths of light, 3 times a week for 3 weeks experienced improved visual acuity and contrast sensitivity with reduced volume of drusen, and that these benefits appeared to last at least 3 months. A new, larger, randomised trial called LIGHTSITE has commenced in Canada, using treatment every 6 months. Results are expected towards the end of 2017.

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.

Treatments of wet AMD

Eye injections for wet AMD using anti-VEGF drugs have now been available for nearly 10 years. These injections have revolutionised the management of wet AMD and are now the standard of care.

Current treatments

The 5 year outcomes of the CATT trial were released in 2016. This showed that in the USA, the longer term outcomes with anti-VEGF injections for wet AMD, while very favourable, tended to drop away after a number of years. This contrasts to Australian results from the *Fight Retinal Blindness!* project published at the end of 2015. This project involves the recording of real world outcomes in thousands of patients over an extended period. This has shown that the Australian outcomes are substantially better than those achieved in the USA or Europe, with most people maintaining vision at or very close to what was achieved in the original clinical trials. The reasons for this are believed to include:

1. Australians received more injections on average than people in the US study
2. Australia has the highest reported awareness of AMD in the world, which is leading to earlier detection of treatable disease, earlier treatment and better results
3. The Australian PBS reimbursement system facilitates good access to affordable treatments
4. Australia has a highly skilled eye health workforce in optometry and ophthalmology delivering quality care.

Anti-VEGF injections in other macular diseases

Currently, anti-VEGF drugs are approved in Australia for treating wet age-related macular degeneration, diabetic macular oedema and retinal vein occlusions. An important study (called MINERVA) released in 2016 using Lucentis injections will hopefully allow its registration and

reimbursement to treat new retinal blood vessel formation (neovascularisation) in a range of other retinal conditions such as myopic macular degeneration, angioid streaks, trauma, and central serous chorioretinopathy. The MINERVA study showed that injections were well tolerated and effective across a range of conditions, and has led to a recommendation for the registration of the drug for these conditions in Europe. The Foundation will be advocating for a similar recommendation to be made in Australia.

Reducing the burden of treatment

Although anti-VEGF injections are highly effective in most people with wet AMD, they impose a significant ongoing treatment burden as they require frequent injections. A large amount of new research aims to reduce treatment burden:

1. Using new delivery devices to provide long-lasting release of the existing drugs into the eye
2. Modifying existing drugs or developing new ones to 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 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.

Gene therapy

A number of companies are making good progress with the insertion of a gene inside a harmless virus shell (or vector) which is then injected into the eye or 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 showed the technique is safe, reduced the swelling in the retina and can reduce the number of injections needed, although the technique still needs significant improvement.

New drugs

A new drug called brolucizumab (RTH-258) has been developed which is an antibody against VEGF that is much smaller than current drugs. The results of the phase 2 OSPREY study were announced in 2016 showing 66% longer average duration of effect with similar visual outcomes compared to existing treatments. Two large phase 3 trials are now underway and due for completion in May 2018. One of these trials includes sites in Australia. The trials include some patients who receive injections every 12 weeks.

A new, tiny refillable micro-pump called Replenish is also being developed which will allow one or more drugs to be slowly released over many months. The pump is placed under the conjunctiva (the thin film covering the front of the eye) and can be programmed to give different quantities of drug at different times.

Another new longer-lasting anti-VEGF drug called abicipar (DARPin) is being tested in two large phase 3 trials which started in July 2015 with injections given every 8 or 12 weeks. These trials are due to be completed in May 2019. One of these trials includes sites in Australia.

Combining drugs

Although excess VEGF protein is a major cause of wet AMD, there are several other proteins involved. Numerous other drugs are being tested to block these other proteins. These would not replace anti-VEGF injections, but would be used in combination

to produce even better outcomes.

Fovista: This drug blocks another protein growth factor called PDGF thereby making leaky new blood vessels more susceptible to the effects of anti-VEGF drugs. In a phase 2 study of 449 patients, injections of Fovista plus Lucentis produced significantly better visual outcomes than Lucentis on its own. There is also good evidence that Fovista may reduce the permanent scarring and vision loss that can still occur with wet AMD, even when injections appear to be working well. Three large phase 3 (registration) studies assessing the use of Fovista in combination with all of the currently available anti-VEGF agents are nearing completion. If successful the treatment may potentially be available in two to three years.

Squalamine eye drops: This is an eye drop that has been shown to further improve vision when given in combination with anti-VEGF injections for wet AMD. While it has both anti-VEGF and anti-PDGF properties, it does not appear to be sufficiently effective on its own, nor does it reduce the number of injections needed. The first of two large phase 3 trials commenced in 2016 and is expected to be complete in 2019.

OPT-302: This new injection is currently in phase 1/2a trials and is targeted towards different VEGF receptors compared to the current agents. It is being developed as a therapy to be used in combination with existing treatments.

Stem cell treatment

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 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.

To give an indication of the scale of the research effort in this field, there are now over 40 institutions and companies that are working with stem cell treatments for AMD and other eye diseases.

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.

Induced pluripotent stem cells (iPSC):

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

Replacing cells

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.

To date, the greatest progress has been made with embryonic stem cells as these are the most adaptable form of stem cell. One company (Ocata) has now been implanting RPE cells derived from embryonic stem cells into people with very poor vision from dry AMD or Stargardt's disease for several years, with no apparent safety issues, and in some people, vision appears to have improved.

Another well-publicised study at the University College in London recently started the use of stem cell derived RPE in people with wet AMD.

Embryonic stem cells however pose ethical issues for some people, so significant effort is being made to 'turn back' certain adult cells (such as skin cells) into stem cells, which can then be reprogrammed into the desired cell such as RPE cells.

To avoid the risk of rejection when cells from one person (the donor) are implanted into another person (the patient or recipient), Japanese researchers at the Riken Institute have successfully taken a patient's own skin cells and converted them to stem cells, which have then been coaxed into retinal cells. These cells have then been implanted into the same person, taking the place of the damaged cells. Unfortunately, this process is very slow and prohibitively expensive.

In 2016, the same researchers are looking at ways to make the technology practical and affordable. They have created banks of stem cells created from skin cells from many donor adults. They then analyse certain

proteins called MHCs on the surface of the cells, which play a key role in the immune response. By matching the MHCs of the donor cells with the MHCs of the patient, they appear to be able to avoid rejection issues and may remove the need for life-long anti-rejection drugs

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. However, to model and better understand the disease process, research in Melbourne is using human stem cell derived retinal tissue. This is important as we do not have a good animal model of the disease process. 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.

Products that have not been successful

Drug development is an expensive, high risk process, and large numbers of treatments fail to demonstrate sufficient efficacy or safety to be registered. During 2016, several potential treatments that have been reported in this summary in previous years have failed to meet expectations and are not being pursued. These include: Emixustat, Isonop, LFG316, Eculizumab, Isonop, Pazopanib, NT-503.

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 almost \$3 million has been committed to leading Australian researchers to undertake exciting and critical research.

A new round of grants will be opened in April 2017.

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.



Our focus is your vision

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