

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.

### Inflammation

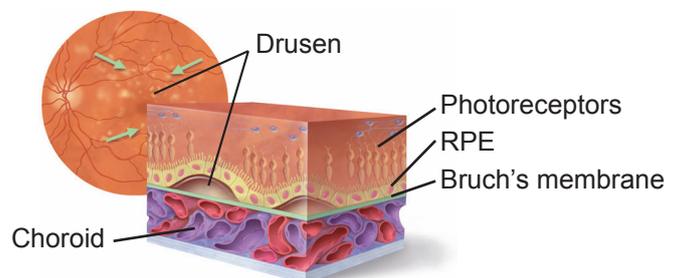
When a group of cells is damaged, the normal repair process involves inflammation. This is a complex process and includes increased blood flow to the tissues. New blood vessels may form, and the vessels can become leaky, leading to swelling. Although inflammation is a normal part of the body’s repair 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 (1.05 mil 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 81,000 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 133,000 Australians have wet MD for which there is effective treatment being 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, and 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
<b>Discovery and development</b>	Usually laboratory work	What causes the disease, identify targets (e.g. find a 'key' that turns off an unwanted process)	Many years
<b>Pre-clinical</b>	Animals or cell cultures	Proof of principle, safety in animals, safe starting dose, toxicity	4 years
<b>Phase 1</b>	20 to 80 healthy volunteers	Safety and dosing	1-2 years
<b>Phase 2</b>	100 to 300 volunteers with disease	Initial efficacy, dosing, larger scale safety	2 years
<b>Phase 3</b>	500 to 3000 volunteers with disease	Detailed efficacy, safety, comparison to other treatments	3 years
<b>Registration and reimbursement</b>		Regulators review studies and detailed manufacturing dossier to decide if treatment should be registered for safety and efficacy and then subsidised	18-24 months
<b>Phase 4</b>	Consenting patients using the test treatment once launched	Long term safety and efficacy	Ongoing

## Assessing 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, 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 2017

### Modelling AMD

As mentioned above, one of the biggest roadblocks in improving our understanding of the precise causes of AMD is the fact that there is no reliable animal model of the disease. The animals commonly used for laboratory research do not even have a macula. It is also not possible to study the disease at the cellular level in living humans without damaging their vision.

To address this, several centres are developing laboratory models of the disease using human retinal cells that have been derived from stem cells. To do this, scientists take skin cells from people with AMD, and then re-program these cells back into stem cells using a technique which earned its developer the Nobel Prize in 2012. These stem cells can then be converted into human RPE cells which are known to play a key role in the development of AMD. These RPE cells grow and multiply in a laboratory dish and can be subjected to various conditions that mimic ageing, so the biological responses

can be studied and compared to cells grown from people without AMD.

In October 2017 the Foundation provided a major grant to advance this area of research focusing on the causes and possible treatments for dry AMD.

## Early detection

Researchers in the US may have found a way to diagnose macular degeneration with a simple blood test. The test involves the analysis of a group of very small molecules in the blood known as metabolites. These are a unique chemical fingerprint and represent the end products of various cellular processes. They are influenced by one's genetics, our environment and micro-organisms in the body. An initial study has shown that the metabolites are significantly different in people with early AMD, and that they vary depending on the stage of the disease. In addition, the test may enable the detection of AMD earlier than with a conventional eye exam.

The Foundation is currently funding an Australian research project in this field which will hopefully confirm the US results and the reliability of the test.

## Disease prevention

An analysis was recently conducted in Melbourne of nine high quality studies published between 1992 and 2016, involving over 40,000 people in Europe, the USA and Australia. This 'meta-analysis' showed that people who maintained an active lifestyle throughout life were 41% less likely to develop late stage AMD, even though their risk of getting the early stages was only reduced slightly. The study authors suggested that even small to moderate amounts of physical activity - as little as three hours per week - may be beneficial. The authors also reinforced the role that physical activity has in reducing the development of other age-related conditions.

## Smoking and AMD

The important role that smoking plays in increasing risk of AMD has been known for decades. Some people may mistakenly think that because they've been smoking for many years, the damage is done and there's no point in quitting. Research released in mid 2017 showed that in fact, it is never too late to give up.

The 5 year follow-up of the CATT trial, which was primarily conducted to compare Avastin and Lucentis for wet AMD, showed that people with wet AMD who received injections but continued to smoke were more than twice as likely to be legally blind after 5 years compared to non-smokers who received injections. Equally important however was that people who quit smoking when they started injections had a much lower risk of being blind after 5 years compared to people who continued to smoke. In fact, after 5 years, the risk of being blind for people who quit was almost as low as people receiving injections who had never smoked. The key message is that it's never too late to quit smoking.

## Early AMD

### 2RT - laser

The use of a new, ultrashort duration laser called 2RT is in the final stages of a phase 3 trial in Australia to see if its previously demonstrated ability to remove or reduce drusen in people with early AMD has any impact on the longer-term progression of dry AMD.

It might seem obvious that removing drusen is a good thing to do, however earlier research has shown that in some people, drusen regress on their own, however the area of regression can be the site of new atrophy of the critical RPE cells. A key question is therefore whether removing drusen with the 2RT laser could actually accelerate atrophy. Although this laser is already available in Australia, its use to

remove drusen must still be considered experimental and treatment should only be performed within a properly conducted clinical trial. The results of the pivotal LEAD trial are expected in late 2018.

## Dry AMD

Dry AMD is a very complex condition and there are many theories explaining how the disease may be triggered and the processes that cause its progression. It is likely that there is no single cause of dry AMD, making the search for treatments more difficult.

Some of the proposed mechanisms include oxidative stress, build-up of fats and proteins producing drusen, overstimulation of the 'complement' pathway of the immune system, chronic inflammation and damage to the blood vessels under the retina in an area called the choroid.

### 'Complement' inhibition

It is generally regarded that overactivity of part of the body's immune system, known as 'complement,' is critical to the development of AMD. The complement system is very complex and has several pathways. A number of proteins are being developed to inhibit different complement pathways in an attempt to reduce the development of dry AMD.

**Lampalizumab:** Is one of the proteins which blocks one particular complement pathway. In a small phase 2 trial, it was shown that lampalizumab could slow down the growth of the diseased area of dry AMD. Unfortunately, when the results of a much larger phase 3 registration trial were released in August 2017, no benefit was seen compared to the use of a placebo.

**APL-2:** A similar protein which acts on different parts of the complement system has also just been reported to have a positive effect in a phase 2 trial, which included several sites in Australia. The drug (previously named POT-4) has been re-formulated and is now called APL-2.

It is given by injection into the eye and was shown to reduce the progression of dry AMD by 29% over 12 months. The manufacturer will be moving forward with phase 3 trials as soon as possible.

**Zimura:** There is a continuation of a phase 2/3 trial in dry AMD of a third complement inhibitor called Zimura, claimed to block all three of the complement pathways. Another study with Zimura in Stargardt's disease is due to start in 2018. Stargardt's is a form of macular degeneration affecting children and adolescents.

**Gene therapy:** A completely different approach for blocking complement overactivity is now being tested with a new gene therapy in an early phase 1 trial. This treatment involves the once-only insertion of a gene that instructs the retina to produce a protein called HMR59. This protein inhibits a chemical called Membrane Attack Complex (or MAC) thereby reducing the stimulation of complement.

**Several other treatments for dry AMD** are being tested including ones which are attempting to protect photoreceptors from damage and others which improve blood flow, and/or the removal of waste from under the retina.

## Wet AMD

Anti-VEGF injections will remain the mainstay of treatment for wet AMD for many years, however several near-term developments are likely to result in the need for fewer injections. Some additional treatments may also be given by eye drops to augment the effect of injections, although drops are unlikely to replace injections in the short to medium term.

### Brolucizumab (RTH258)

The results of two large phase 3 (registration) trials for a new eye injection for wet AMD called brolucizumab were announced in June 2017. Both studies compared brolucizumab with an existing registered treatment (Eylea) over a period

of 48 weeks. The new agent demonstrated impressive vision outcomes which were comparable to Eylea, and over 50% of people receiving brolocizumab were able to have the duration between injections increased to 12 weeks, compared to the typical 8 weeks between Eylea injections. Results from these studies will enable brolocizumab to be submitted for registration in 2018, after completion of other studies regarding the production methods.

### Abicipar (DARPin)

Phase 2 trials for this drug, also given as an eye injection for wet AMD, were very promising, suggesting longer duration of effect and improved efficacy compared to current treatments. These results now need to be confirmed in Phase 3 trials which are underway and due to be completed in 2019. These trials are fully enrolled and are comparing 8 and 12 weekly dosing versus monthly treatment with Lucentis.

### OPT-302

Current injections for wet AMD block a protein called VEGF-A. A new treatment developed in Australia called OPT-302 blocks two related proteins, VEGF-C and VEGF-D, which may also play a role in the formation of new blood vessels. In 2017, a phase 1/2 study using OPT-302 in combination with an existing treatment suggested a worthwhile additional effect with a good safety profile. In addition, people who had responded poorly to the existing treatment on its own appeared to do better with combination therapy. These results have enabled the product to be moved into the next phase of research.

### Fovista (pegpleranib)

In last year's edition of this update, it was reported that another treatment, Fovista, intended for combination therapy, was nearing the end of phase 3 trials. Despite very promising earlier studies the phase 3 trials did not show any benefit of the treatment compared to placebo.

## Eye drops for macular conditions

Substantial research effort is being made to develop treatments for wet and dry AMD in an eye drop which could be self-administered. Although there are several eye drops available to treat conditions at the front of the eye, there are many additional challenges in delivering an adequate dose of a drug to the back of the eye. It is also critical that the drops penetrate the cornea quickly, or else the drug will be washed away by the person's normal tears. Many eye drops have shown success for retinal conditions in animal models but have proven to be ineffective when used in humans for retinal diseases. Two treatments that appear to be overcoming these issues are:

- a) **Cell-penetrating peptides** - these are similar to proteins, but much smaller, and when used as an eye drop, are able to carry a 'cargo' of an existing drug, such as an anti-VEGF agent, through the cornea, the jelly inside the eye and into the cells in the retina at the back of the eye. British researchers have shown that when given once per day, these eye drops enable a therapeutic dose of the drug to be delivered to the retina of several animal models and human cell cultures, without causing damage to the cells. Trials in humans will now be required.
- b) **Squalamine** - while a phase 2 study showed that this eye drop, given in combination with eye injections for wet AMD, did not reduce the number of injections required, it did result in better visual acuity outcomes. The drug is now undergoing an initial phase 3 trial called MAKO which is expected to be completed by early 2018. If positive, a further phase 3 trial will likely be required to enable registration.

## 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.

### 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 cells can be re-programmed to revert back to being a stem cell. These 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.

### Ocata, Japan and USA

Arguably the most advanced treatment in this field is by Ocata (formerly Advanced Cell Technologies). This uses RPE cells derived from a single embryonic stem cell, and human trials in dry AMD and Stargardt's disease have now progressed to phase 2. The technology appears to be safe, with the RPE cells remaining very stable with no evidence of cells changing or growing out of control. There has been some suggestion of an improvement in vision, although to date, studies have been focusing on safety rather than efficacy.

### Riken Institute, Japan

This group has been developing induced pluripotent stem cells to produce RPE cells. The first human trial of this was in 2014, when stem cells were created from the patient's own skin cells. The process was very time-consuming and extremely expensive, but was well tolerated and showed some evidence of preserving vision. In 2017, in order to make the treatment more cost effective, the research group created a bank of stem cells from dozens of adult donors. These stem cells were then reprogrammed to become retinal cells. To reduce the risk of tissue rejection, these cells are then matched to the recipient based on the composition of certain proteins on the surface of the cells. This process

means that the recipient should only require small doses of anti-rejection drugs. In March 2017, the first human received induced pluripotent stem cells from another adult.

### **The use of undifferentiated stem cells - a dangerous practice.**

All of the serious, legitimate research in this field involves the use of stem cells that have been differentiated (converted) into specific retinal cells, prior to implantation into humans. At this time, none of these studies are in Australia.

Some foreign companies have been capitalising on the excitement surrounding stem cells by aggressively promoting and selling unproven but very expensive “treatments” that involve the implantation of undifferentiated stem cells into the eye, and falsely claiming that this is research.

These undifferentiated cells can potentially turn into any type of cell, including cancer cells, and there have been several recent tragic cases in the USA where people have been blinded by this kind of treatment. Laws are now being introduced in the USA to prevent this from happening again, but it

is possible that unscrupulous operators in other countries may continue the practice.

**The Foundation would like to stress that, at this time, there are no registered (approved) stem-cell based treatments for retinal conditions available anywhere in the world. Several more years work is required before any stem cell treatment is expected to gain registration and become readily available.**

**Indeed, before considering any “unusual treatment”, you should always discuss the evidence with your ophthalmologist.**

### **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 call on 1800 111 709 or visit the Foundation’s website.

## **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, \$3.6 million has been committed to leading Australian researchers to undertake exciting and critical research. Further details of the Foundation’s research grants are available on the Foundation’s website.

**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](http://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

**For further information and support, or a free information kit, call the Foundation’s Helpline 1800 111 709 or visit [www.mdfoundation.com.au](http://www.mdfoundation.com.au)**