Macular Disease Foundation AUSTRALIA™

Our focus is your vision

Macular Degeneration Research Update December 2013

Macular degeneration (MD) is the leading cause of blindness and severe vision loss in Australia. A major global research effort is underway to better understand the disease, how it can be treated, and eventually cured. Australian researchers, many of whom are supported by the Macular Disease Foundation Australia Research Grants Program, are at the forefront of this endeavour. This update gives an overview of some of the directions of research that may provide the answers needed to eventually conquer this disease. Note that many of these treatments are still many years from registration and availability.

How does macular degeneration develop?

Oxidative stress

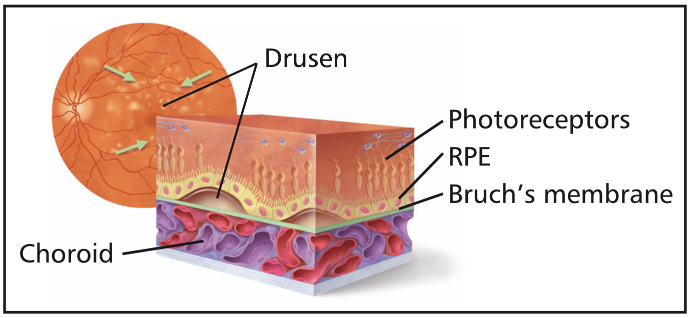
All cells obtain energy by combining the nutrients from digested food with oxygen from the bloodstream. This process produces toxic waste products called free radicals, which can cause "oxidative damage" to the cells. This can be thought of as a type of rust. Eating a healthy diet rich in anti-oxidants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

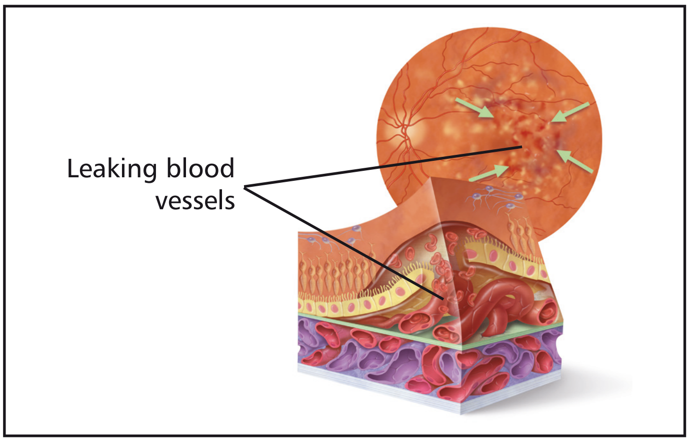
How does this relate to macular degeneration?

In people with MD, 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. However, many of the processes involved remain unclear. 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 MD. About 12% of Australians over 50 (860,000 people) show evidence of early MD 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 **dry macular degeneration** and the late stage is called **geographic atrophy**. About 60,000 Australians have late stage dry MD, 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 wet MD.** About 110,000 Australians have wet MD and there is currently effective treatment using anti-VEGF drugs.



What is the influence of genes?

A large number of genes have been identified which can significantly affect the development of MD, either slowing it down or speeding it up. Some people carry one or more gene variations which affect a part of the immune system called 'complement'. This plays a major role in inflammation and blood vessel formation. Other genes may affect the way we convert food, or how the body manages waste products.

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.

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

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 efficacy	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

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.

What happens to make drugs affordable in Australia?

Following registration, the Pharmaceutical Benefits Advisory Committee (PBAC) reviews additional data regarding the safety, efficacy 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 remainder being subsidised by the taxpayer.

Research highlights 2013

Diet and supplements

AREDS2 results

One of the most anticipated studies reported in 2013 was the Age-Related Eye Disease Study 2 (AREDS2), conducted by the US Government's National Institutes of Health (NIH).

This follows the original AREDS study conducted in 2001 which showed that for certain people, a supplement based on a specific formula of zinc and antioxidants can reduce the risk of progression of AMD. For people in the intermediate stage of AMD in one or both eyes, or in the late stage in one eye only, the AREDS formula reduced the risk of progression of the disease by 20 to 25% and delayed vision loss. In May 2013, the NIH researchers announced the results of their follow-up study, AREDS2. This was a 6-year study involving over 4,200 patients, who took various modifications of the original AREDS formulation.

The main recommendation from AREDS2 was for the continued use of the original AREDS formulation, but with beta-carotene removed, to be replaced by lutein/zeaxanthin.

The AREDS2 formulation as recommended by the US National Institutes of Health is the following (daily dose):

Zinc (as zinc oxide)	**80 mg**
Vitamin C	**500 mg**
Vitamin E	**400 IU**
Copper (as cupric oxide)	**2 mg**
Lutein	**10 mg**
Zeaxanthin	**2 mg**

This was shown to be of benefit for those people with the intermediate stage of MD in either eye or with late MD (ie geographic atrophy or wet MD) in one eye only.

AREDS 2 and fish oil

AREDS2 also showed that in a study population which was well nourished with good dietary intake of omega-3s, an additional daily dose of the omega-3s DHA (350 mg) and EPA (650 mg) did not appear to provide any additional benefit. Other researchers are now examining if a different dose or ratio of omega-3s may provide some benefit. There is however a large body of evidence that eating actual fish is beneficial to reducing the risk of MD.

AREDS 2 and zinc

AREDS2 also examined whether reducing the zinc dose was of any benefit. The study suggested a slightly reduced effectiveness with the lower dose, however the study was not large enough to say that this was a true difference or just a chance result. The study showed that both doses were tolerated equally well. In addition, a 10 year follow-up of the original AREDS trial showed that the 80 mg daily zinc dose continued to be well tolerated. As such, the AREDS2 investigators recommend that there is no good reason to change to the lower dose as it doesn't appear to offer any benefit, and it might be slightly less effective.

An updated Nutrition and Supplements fact sheet is available from the Foundation. Please call 1800 111 709.

Saffron

To date, there is no conclusive evidence that saffron has any effect on MD. Some preliminary work has shown that saffron appears to affect some of the electrical properties in the retina and it may help retinal cells recover from certain types of injury. Research is currently underway on the effect of saffron on the development or progression of MD.

Treatments for early and dry MD

At this stage there are still no effective treatments for early stage MD or for dry MD other than diet and lifestyle measures.
Why is this?

1. We still don't fully understand the various mechanisms causing early and dry MD.

2. Early and dry MD normally develop over many years or decades so it can take a long time to evaluate if any treatment is working.

3. The genetics of MD is very complex. At least 20 genes appear to be involved, but some genes increase risk, while others may be protective. More genes are being discovered all the time.

4. There is no reliable "test-tube" or animal model of early or dry MD to test new theories or treatments before they can be tested in humans. For example, many theories and treatments have shown great success in mice or rabbits, but have been unsuccessful when tried in humans.

However, it is encouraging that there has been major progress with dry MD research in recent years and several new treatments are expected to become available in the next few years.

2RT laser

Previous research demonstrated that an ultra-short duration laser, developed in Australia, could safely remove drusen. A world-first, randomised trial of 240 patients is now underway to see if removing drusen with this laser in people with the early signs of disease is able to slow or halt the progression of AMD. The trial has now been running for a year and about 100 patients have already enrolled in the planned three year trial. Half of the patients receive the laser treatment and half receive a placebo or "sham" treatment.

Emixustat (ACU-4429)

In May 2013, it was reported that in a phase 2a study, 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 toxic waste that builds up in drusen. By slowing down rod function, this waste production appears to be reduced. A side effect is a slowing of one's ability to adapt to darker conditions, but treatment was otherwise well tolerated. A long-term phase 2b/3 trial began in 2013 to measure if this reduced rod function reduces the generation of waste and slows the progression of MD.

MacuClear (MC-1101)

This is an eye drop version of a drug that is already in use for reducing high blood pressure. It is believed that the drug improves flow in the blood vessels (choroid) under the retina and will help to prevent the excess debris that builds up in dry MD. As the drug has already demonstrated good safety, studies have been accelerated. This is now in an initial phase 3 study to be completed in 2014. If positive, a second phase 3 study in 500 patients will follow.

Complement inhibitors

It is known that one of the major contributors in the formation of dry MD is the malfunctioning of part of the immune system, known as complement. The complement system helps or "complements" our antibody defence mechanism. Complement consists of over 25 small proteins in the blood; these proteins will multiply dramatically in response to certain triggers and produce other chemicals which can destroy bacteria or other unwanted material. Some people carry one or more genes which affect one's ability to regulate the complement system. In some cases, this leads to overactivity, significant inflammation and progression of AMD. To date, none of the complement-based therapies have progressed to phase 3 trials and many projects have ceased due to poor results. This possibly highlights that there is not a full understanding of the underlying disease process. Some of the projects in the complement area which continue include the following:

a) MorphoSys (LFG316)

This is an antibody against C5, one of the factors involved in the complement system. A phase 2 study involving monthly eye injections in people with late stage dry MD is due for completion in mid 2014 to ascertain if the treatment can reduce vision loss.

b) Lampalizumab (FCFD4514S)

This drug is an antibody targeting complement factor D. In August 2013 it was reported that this treatment, given as an eye injection every month to people with advanced dry AMD (geographic atrophy), showed a 20.4% reduction in progression of the scarred area at 18 months. In people with certain characteristics, a 54% reduction in progression was seen. Another study, due for completion at the end of 2016, is assessing long term safety.

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.

Treatments for wet MD

There is already a number of highly successful treatments for the more aggressive 'wet' form of MD. Research continues to produce treatments which last longer or which may reduce the need for regular injections.

Fovista (E10030)

This drug blocks another growth factor called PDGF, which is involved in the formation of unwanted blood vessels behind the retina. In late 2012 it was reported that this treatment, given as an eye injection in 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. The drug was well tolerated. A large, 12 month, phase 3 (registration) study in 1900 patients new to treatment is planned and if positive, this drug could be available within 3 years.

Pazopanib

This drug is already available in much higher doses for the treatment of certain cancers. It inhibits both VEGF and PDGF. In a small study published in October 2013 to determine possible dosing levels, a tablet version of this drug was well tolerated and importantly, demonstrated improvement in vision and reduction of retinal swelling in most people taking the tablets. Most people did not require any "rescue" anti-VEGF injections. A subset of patients did not do as well; these all carried a particular high risk gene. A larger, longer-term study is now being planned.

Squalamine

Some years ago, this treatment was shown to be effective against wet MD when given as a weekly intravenous infusion, however this means of administration was considered impractical. The development of a daily eye drop followed. Squalamine counters the effects of several wet MD growth factors including VEGF, PDGF and bFGF.

In 2013, it was reported that a large phase 2 trial of squalamine daily eye drop was progressing well. It is not clear if this treatment could totally replace injections, but if it reduced the number required it would be a highly positive outcome.

DARPin

This is a new class of engineered small proteins which are designed to copy the effects of antibodies. They are given by injection into the eye. Pre-clinical and early human trials indicated that they have very high potency, with a long duration of effect, however in 2013 it was announced that the mid-stage trial results did not warrant an immediate move to late stage trials. If the drug proceeds, it will not be available until 2019 at the earliest.

X-ray treatment

Several new types of X-ray treatment are being investigated in people with wet AMD to see if the number of injections can be reduced. These treatments deliver a low energy, highly targeted dose of X-ray to leaking blood vessels. In 2013, it was shown that when used in people new to injections, one of these X-ray treatments was not able to reduce the number of injections. This treatment has now been discontinued.

When used in people who had already been receiving injections for about a year, a slightly different X-ray treatment called IRay resulted in a modest average reduction of about one injection in each of the first and second years. The treatment was generally safe in the short term, although one patient out of 147 receiving the IRay therapy experienced a serious complication called radiation retinopathy. Longer term monitoring will be required as this complication can occur many years after IRay treatment. This treatment has recently become available in the United Kingdom, but is not yet in Australia.

Treatments for dry and wet MD

Significant progress is being made with gene therapies along with stem cell treatment and other technologies which will hopefully be able to restore some sight in people who have lost significant vision.

Gene therapy

One of the most promising areas of research in AMD and several related macular conditions is in gene therapy. Our genes can be thought of as books of instructions, telling the body how to do certain things, such as respond to injury.

Gene therapy involves the insertion of a desired gene inside a safe virus "vector" (carrier). This vector can then be implanted into the target area, such as under the retina, where the desired genes become incorporated inside the cells. Here they can instruct the cells how to respond to the disease. There are two main types of gene therapy being developed:

1. The first is where there is a known gene defect causing the disease. A correct version of the gene can be implanted into the affected organ or tissue, such as the retina, effectively taking over the function of the defective gene.

This approach is being used with a treatment called **Retinostat** for MD and a similar treatment called **StarGen** for Stargardt's disease, a form of MD that affects younger people. It is hoped that StarGen may also be suitable for some people with dry MD.

2. The second type of gene therapy involves the insertion of a gene which is able to stimulate the long-term production of a therapeutic protein, such as an anti-VEGF agent, thereby taking the place or reducing the need for regular anti-VEGF injections.

In May 2013, Australian researchers announced that their vector, known as AVA-101 has successfully and safely enabled the insertion of a gene that stimulates anti-VEGF production under the retina in six people with wet AMD. This resulted in apparent improvements in visual acuity and a substantial reduction in the need for injections.

Initially, the technique involved delicate surgery to transplant the vector underneath the retina. In June 2013, it was announced that more than 100 million variations of the virus vector have now been tested, and certain examples have been chosen which are able to migrate under the retina when simply injected into the middle of the eye. This will avoid the need for more complicated surgery.

Based on earlier animal studies, it is believed that a single injection of the gene therapy could provide treatment for many years, and possibly for life. Although this treatment has shown good safety so far, it is important to know whether the long-term production of an anti-VEGF protein will have any negative effects, so longer term research with more patients is still needed.

Stem cell treatment

Stem cells are special types of cells that are able to transform into other types of cell.

The main purpose of stem cell treatment will be to replace damaged or dead retinal cells in people who have already lost vision. Human trials have already started using RPE cells derived from stem cells. RPE cells provide support for the overlying photoreceptors which are also typically damaged in late stage MD. It is likely that ultimately, both RPE and photoreceptors will need to be replaced to provide significant restoration of vision. The development of photoreceptors from stem cells is many years behind the development of RPE cells, however in 2013, for the first time, scientists in the United Kingdom have implanted photoreceptors derived from stem cells into blind mice and restored vision.

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 transformed into the desired cell

type. hESCs are generally considered to be 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, when compared to hESCs.

Some current trials on stem cells

1. Advanced Cell Technologies (ACT), USA

ACT has been able to culture huge quantities of stem cells from a single hESC. They have then coaxed large numbers of stem cells into becoming RPE cells. Human trials with RPE cells implanted under the retina started in 2011, in small numbers of patients with very poor vision from advanced dry MD or Stargardt's disease. Initial studies are primarily testing the safety of treatment. New patients are receiving progressively larger numbers of implanted cells. To date, no safety issues have been identified. The implanted cells are stable, and are remaining in place. In May 2013, the company reported that one patient has shown an improvement in vision from 6/120 (legal blindness) to 6/12 (driving vision), a remarkable and unexpected result. It is not yet known if other patients will experience such dramatic improvement.

2. StemCells Inc, USA

This company is now assessing the safety and signs of visual benefit of human neural stem cells (HuCNS-SC) implanted into the retina of 16 patients with dry AMD. Previous research with rats has shown that these cells are able to survive for long periods, protect photoreceptors and preserve vision. Patients will be followed for 5 years to ensure long term safety and efficacy.

3. Riken Research, Japan

The Riken group received approval in 2013 to commence human trials of retinal cells derived from a type of stem cell found in the patient's own skin. This approach should avoid the potential issue of rejection that could occur with stem cells from another source. The Japanese government is providing substantial funding for this research.

Other human stem cell trials are also underway in Brazil and South Korea.

4. Centre for Eye Research Australia (CERA), Melbourne

Although there are presently no Australian human trials of stem cell-derived treatments for MD, CERA is currently taking skin cells from humans who have various eye diseases, including MD, and are turning these into stem cells which are then coaxed to become retinal cells grown in a dish. These cells are then being used as a "live" laboratory model of the human retina to gain a more accurate understanding of the causes of eye diseases. These cells could also be used as an early "test bed" for potential treatments before entering clinical trials in actual humans.

IMPORTANT NOTE ON 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.

- There are currently no commercially available, registered stem cell-derived treatments for MD available anywhere in the world.
- Please take heed of the Foundation's warning that in countries with poor regulatory controls, there are unscrupulous companies that are selling unproven and unregistered 'treatments' using products that they claim to be stem cells.
- The Foundation strongly advises all patients to discuss any treatment considerations with their eye specialist.

Implantable telescope

A miniature, implantable telescope is now available in the USA. To implant this, the surgeon removes the lens from inside the eye (as occurs when you have a cataract removed) and instead of replacing your lens with a new plastic lens, a tiny telescope, smaller than a pea, is implanted. This is only placed in one eye as it will remove the peripheral vision in that eye. Disadvantages include high cost, 6 to 12 months of specialised training in the USA and limited magnification.

Bionic eye

Several artificial retinal implants (or bionic eyes) are being developed. Most of these devices use a camera, mounted on a pair of glasses, to convert an image into an electrical signal which stimulates a series of electrodes on or behind the retina. This is then interpreted by the brain as a simple image. These devices are currently not suitable for people with MD. It is hoped that in perhaps 10 years, improvements with the device will enable use in people with late MD.

SUPPORTING RESEARCH

"There have been great steps forward in diagnosis and treatment of macular degeneration since I was diagnosed over 20 years ago. It saddens me that current treatments and information were not available for me and many like me who have vision loss or are legally blind. However, I know the answer is to help fund research, so that my children and grandchildren, and all Australians, will be able to see a future without macular degeneration."

Jean Morton – Friend of the Foundation

To donate to the Macular Disease Foundation Australia Research Grants program, please call 1800 111 709.

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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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

December 2013