Macular Degeneration Foundation®

Our focus is your vision

Research Update December 2012

This update is a summary of some of the latest developments in Macular Degeneration (MD) research. This is an area of significant investment and effort, and some research projects are showing great promise. Please note that most of the treatments discussed are still many years from registration and availability.

Background

When discussing research for MD, it is important to have a basic understanding of what is happening inside the eye, including the retina and central macula, as the disease develops.

Oxidative stress

The cells in the eyes obtain energy by combining digested foods with oxygen from the bloodstream. This process produces toxic waste products called free radicals which can cause "oxidative damage" to the cells. A person eating a healthy diet is normally able to eliminate or neutralise these free radicals and repair any damage that has occurred. When the metabolism gets out of balance from additional toxins it can suffer from 'oxidative stress'.

Inflammation

When a tissue is damaged, the normal repair process may involve inflammation. Inflammation affects many things including the blood vessels to the tissues. Blood flow increases, and the vessels become leaky, leading to swelling. Although inflammation is a normal part of the body's repair mechanism, if prolonged, it can lead to many problems.

How does this relate to Macular Degeneration?

A combination of oxidative stress and inflammation are important factors causing damage or death to certain cells in the retina of MD patients. However, many of the processes involved remain unclear.

Waste products inside the eye 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 these waste products are not cleared away, they can form deposits called drusen. These deposits are a sign of **early MD.** Drusen 'clog the system' and can also decrease the delivery of nutrients and oxygen to RPE cells and the photoreceptor cells. In some people, these changes eventually cause the death of these cells, producing 'worn out' patches (atrophy) and loss of central vision. **This is dry MD.**

One of the responses to the lack of oxygen can be the increased production of several proteins including vascular endothelial growth factor (VEGF), which stimulate the production of additional blood vessels. In some people the growth of new vessels gets 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 cell death and significant vision loss. **This is wet MD.**

The influence of genes: Researchers have now identified a large number of genes which can significantly affect different steps in this process. For example, some people carry one or more damaged genes 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. People carrying certain genes are much more likely to experience disease progression and vision loss.

Medical research phases

This table shows the different stages involved to bring a new drug to a point where it can be approved for use. Patient numbers and study durations can vary greatly.

Research phase	Patients studied	What studied	Average duration
Discovery	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

The development of treatments

MD results from a very complex cascade of events with many factors impacting upon each other. While it has been possible to develop treatments that affect a part of the process, no treatment has been able to alter the entire process. This means that so far, the disease can be slowed down but not stopped or cured.

Early and Dry Macular Degeneration

12% of Australians over 50 years (856,000 people) show evidence of early MD. This involves fatty deposits (drusen) under the RPE layer of the retina. Normally there are no symptoms with early MD, but there is a risk of progression.

Nearly 60,000 Australians have late stage dry MD (also called geographic atrophy). Dry MD involves thinning of retinal tissue, normally producing gradual loss of central vision. There are currently no treatments for early MD or dry MD. Presently, the only way to slow disease progression is through diet and lifestyle changes.

Why is it taking so long to develop treatments for dry MD?

- Dry MD is a very complex disease with many genetic and environmental factors contributing to its formation. Detailed understanding of these factors and how they influence each other is still not completely known.
- Dry MD typically develops very slowly, often over decades, so it can take a long time to evaluate if an intervention is having any effect on vision.
- There are no reliable systems for testing the efficacy of drugs for dry MD 'in the test-tube' or in animals before the drugs enter human trials. A well-developed macula is only found in primates and birds, and while numerous attempts have been made to develop animal models for MD, none of these truly replicate the disease process in humans.

Dry MD treatments in development

2RT™ laser

This involves a potentially new treatment for early Age-related Macular Degeneration (AMD) using an ultra-short duration, low energy laser, which has been developed in Australia. After a successful pilot study, in which the laser was shown to safely remove drusen, a world-first randomised controlled trial of the laser in early AMD, is now being conducted. A number of sites across Australia will be involved.

Previous trials of a stronger laser for early AMD showed that it was effective at removing drusen but in the long term there were more complications in the treated patients with no long-term visual benefit. It is hoped a softer laser will have a better outcome but it will take years to find out. To minimise risk only one eye will be treated.

ACU-4429

Given as a tablet, this drug slows down the activity of photoreceptor cells and therefore the production of waste products such as lipofuscin and A2E, which are believed to be critical in the progression of dry MD. In 2012, the first human studies have shown that the drug does slow down the activity of photoreceptors, confirming animal trials. Studies are now needed to see if this translates into a slowing of disease progression. If successful, this drug may also be of benefit for younger people with the early stages of Stargardt's disease.

AL-8309b (Tandospirone)

A large phase 3 trial of 772 patients with dry MD was completed in May 2012. This agent, given as an eye drop, protects the retina from oxidative damage. Results are currently being analysed.

MacuClear (MC-1101)

This treatment has previously been studied and approved for another use, with a good safety record. It is now about to commence a phase 2/3 study as a treatment for dry MD. It is claimed that the treatment improves blood flow in the choroid underneath the retina. It has also been shown to possess anti-inflammatory and anti-oxidant properties.

Glitiramer (Copaxone)

This agent is able to modify the immune system in several ways and has already been shown to be safe and effective in another disease involving serious nerve degeneration. An initial study in people with dry MD showed a 53% reduction in drusen area after 12 weeks. A new, larger phase 2/3 study commenced recruiting patients in 2012. This aims to confirm the effectiveness in arresting the spread of dry MD as well as the rate of progression to wet.

RN6G

A phase 2, randomised, placebo-controlled trial with RN6G commenced in August 2012 in people with the late stage of dry MD. These people are at particular risk of losing significant extra vision. Treatment is given as a monthly intravenous drip. The study will assess the size of the area of cell loss and measure visual activity outcomes. Results are expected in 2014.

Some other treatments in development for dry Macular Degeneration

Agent	Stage	Form
AREDS-2 (supplement)	3	Tablet
ARC-1905	1	Eye injection
NT-501	3	Implant
Brimonidine	2	Implant
Iluvien	2/3	Implant
AL-78898A	2/3	Gel eye injection
GSK933776	2	Intravenous infusion
Sirolimus	1/2	Intravitreal injection

Wet Macular Degeneration

About 110,000 Australians have wet MD. Wet MD involves the formation of leaky blood vessels under the retina, typically producing rapid loss of vision. Treatment is available with the best results seen in people who start treatment soon after bleeding starts. Early detection is vital. Disease progression can also be slowed through diet and lifestyle changes.

Wet MD treatments in development

Fovista (formerly E10030)

In June 2012, the results of a phase 2b study of 449 patients with wet AMD were released in which Fovista combined with Lucentis was shown to provide significantly better visual acuity gains when compared to Lucentis on its own. Whereas Lucentis targets VEGF, Fovista targets another growth factor called PDGF-B which is believed to also play a role in the formation of new, leaky blood vessels. This approach highlights that further improvements in treatment are likely to come from the use of combination therapy, similar to how treatment is being improved for many other diseases such as cancer.

Squalamine

An earlier version of this drug has already been shown to affect multiple growth factors and to be effective in stopping the growth of new blood vessels in MD. It has now been developed so it can be administered via an eye drop. The US Federal Drug Administration (FDA) has granted the treatment a 'fast track' designation. This means it will accelerate the review of data to keep the research program moving quickly. A phase 2 study is starting in late 2012. All patients will receive a single injection of Lucentis, and then daily, self-administered eye drops of Squalamine to determine whether they will need further retreatment with Lucentis.

AGN 150998 and MPO260

These agents are from a new class of drug called DARPINs. In pre-clinical studies, they have been shown to have high effectiveness and long duration of effect. DARPIN drugs affect growth factors such as VEGF-A and PDGF-B. One of these has successfully completed phase 2a trials with no safety issues, showing a good demonstration of effectiveness when injected into the eye with dosing intervals of up to three months. Further trials are underway.

Some other treatments in development for wet Macular Degeneration

Agent	Stage	Form
Pazopanib	2	Eye drop
AL-39324	2	Eye injection
Everolimus	2	Tablet
iSONEP	2	Eye injection
Combretastatin	2	Infusion
ATG-3	2	Eye drop
Sirolimus	2/3	Eye injection

Dry and Wet Macular Degeneration

Gene therapy

Despite some setbacks in the 1990s, gene therapy is rapidly emerging as one of the more promising areas in the management of MD. Gene therapy possibly represents the most likely approach for an eventual cure for the majority of AMD cases as it can potentially repair or replace the faulty gene(s) that lie at the heart of at least 70% of cases.

Gene therapy can take several forms. It can firstly be used to replace a defective gene with the correct gene inside a cell or group of cells such as the eye's photoreceptors or RPE. It can also be used to insert a gene which stimulates the production of a therapeutic protein, effectively taking the place of drugs.

Gene therapy involves the insertion of desired genes inside a tiny, safe virus, which has had its own DNA removed. This virus "vector" (carrier) is then injected into the desired area and the new genes become incorporated into the cells. A major benefit of gene therapy is that one dose may provide treatment for many years and possibly for life. One risk however is that it may not be possible to "turn off" the implanted gene if its effect is no longer needed or if it causes major side effects. There are currently a number of gene therapy programs underway for MD.

AVA-101

This is one of the most advanced gene therapies in Australia and is now being tested in Australia in a phase 1/2 study for people with wet AMD. A vector is injected into the eye which inserts a gene that stimulates the production of an anti-VEGF, potentially eliminating the need for injections.

Retinostat

A similar treatment to AVA-101called Retinostat is in phase 1 for patients with wet MD and Phase 1/2 for Stargardt's disease.

The first human results in 2012 show that the treatment appears safe at low doses. Further people are now being treated with higher doses to ensure safety is maintained at therapeutic dose levels. Previous animal studies showed that the treatment is able to "express" (generate) therapeutic protein levels after a single injection.

Stem cell treatment

Stem cells are special types of cells that are able to transform into other types of cell. There are several potential 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 quite limited in the types of other cells they can produce.

3. **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, albeit with less flexibility than hESCs.

The main role of stem cell treatment will be to replace damaged or destroyed retinal cells in people who have already lost some vision. Initial stem cell treatments will aim to replace RPE cells which provide support for the overlying photoreceptors. It should be noted that photoreceptors are also typically damaged in late stage MD. Ultimately, both RPE and photoreceptors will need to be replaced to provide significant restoration of vision. Photoreceptors are much more complex than RPE cells, and the development of photoreceptors from stem cells is many years behind the development of RPE cells.

There are currently at least seven companies that are now conducting or are about to start human trials of stem cell treatments for macular degeneration. Many more are at the pre-clinical stage. The following are some examples of such stem cell research projects.

Advanced Cell Technologies (ACT)
In early 2012, ACT reported the first ever results of implanted RPE cells derived from ESCs in people with advanced dry AMD and Stargardt's disease. Initial studies in the USA and UK are in a small number of people with very poor vision, and are only designed to assess the safety of treatment. Very early results show that low doses of implanted cells are well tolerated, remain in place and do not grow out of control. Further patients will now receive progressively higher doses of cells to confirm safety and assess effectiveness. It is hoped that ultimately, people can receive RPE cells earlier in the disease process, before their photoreceptors have been destroyed.

The London Project to Cure Blindness
The first phase of this project, being undertaken in the United Kingdom, has successfully developed RPE cells from embryonic stem cells. The regulatory requirements are currently being addressed for an application to start human trials in 2013. Phase 2 of the study will involve the creation of individualised stem cells from each patient that has AMD. The patient's own stem cells, taken from a blood sample or skin snip will be used to make personalised RPE cells for transplantation. This will be closer to a perfect match between the patient and the transplanted cells. In the longer term the project also aims to develop photoreceptor cells derived from stem cells.

Riken Research
The Riken group will be working with Dr Shinya Yamanaka, who jointly received the 2012 Nobel Prize for medicine for his work showing that adult cells can be re-programmed to become stem cells. Riken plans to commence human trials in 2013 using RPE cells derived from induced pluripotent adult stem cells. This group has previously grown an entire mouse retina from stem cells.

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.

Implants and retinal replacement

Several companies, including two in Australia, are developing artificial retinal implants (often called bionic eyes). These devices typically involve the use of an external camera, normally located on a pair of glasses. This is linked to an implant located on or behind the retina.

The camera converts the visual image into an electrical signal which is then transmitted to the retinal implant. The retinal implant stimulates the nerves going to the brain, creating a simple image.

The first generation of these devices are already available in Europe, however they can only produce basic, fuzzy images such as the location of a doorway. They could be of significant value to people who are totally (black) blind. Advanced MD results in loss of central vision and not total blindness. Although the resolution of retinal implants and other forms of 'artificial vision' will improve, it is unlikely that these technologies will be relevant to MD patients for at least 10 years.

Macular Degeneration Foundation Research Grants Program

In 2011, the Macular Degeneration Foundation commenced funding for two major research projects. A research fellowship, kindly funded by Blackmores and The Blackmore Foundation, also commenced. Here is a brief summary of progress to date.

Professor Robyn Guymer - Centre for Eye Research Australia (CERA), Melbourne

Whilst 1 in 7 people over the age of 50 have the early signs of AMD, not everyone progresses to vision loss. Determining those with early AMD most likely to progress to vision loss is presently a very inexact science. The aim of this project is to identify characteristics of AMD that determine who is most likely to progress to the late, vision threatening disease.

People with various stages of AMD are being enrolled in this 'natural history' study. Once enrolled, each participant is evaluated every 6 months for 18 months using a variety of new and existing diagnostic techniques to determine how they have progressed over time.

To date, one scientific paper has been submitted describing a novel appearance on an OCT scan that appears to correlate with poor macular function. This is an important finding as it may mean a relatively simple diagnostic test may provide a marker of the retina's health and how 'at risk' the eye might be for losing vision. This is the first time this finding has been reported.

Professor Paul Mitchell - Westmead Millennium Institute, Sydney

The aim of this study is to gain a deeper understanding of the risk factor profile of people who are seeking treatment for late-stage AMD. This will build on the invaluable data obtained from Professor Mitchell's world acclaimed Blue Mountains Eye Study. The study is assessing the impact of AMD on quality of life, identifying the prevalence of AMD specific genes and determining the primary barriers to accessing treatment.

Importantly, this study will shed new light on the link between modifiable risk factors (e.g. nutrition, body weight and smoking) and non-modifiable factors (e.g. genetic predisposition). A key outcome of the research will be an enhanced capacity for early identification of people at a high risk of disease progression. People at higher risk will be better equipped to modify their lifestyle in order to slow the progression of their disease and improve their quality of life.

Blackmores Dr Paul Beaumont Research Fellowship Dr Liubov Robman - CERA, Melbourne

Dr Robman has been working on the analysis of the Melbourne Collaborative Cohort Study (MCCS), which is the world's largest study of risk factors. Research has revealed a different rate of AMD in relation to the ethnicity of participants. This is important, as a large (14% proportion) of participants were first generation migrants from Greece or Italy. They have different lifestyle and dietary traditions and come from a different genetic pool than the other participants that are Anglo-Celts born in Australia, UK or New Zealand.

Detailed analysis of the diet of over 40,000 participants in the study has identified 6 broad dietary patterns, one of which, based predominantly on a diverse combination of fish, vegetables, rice, nuts and chicken was associated with a 35% lower risk for late AMD. Other dietary influences on AMD continue to be studied.

Donate to the Macular Degeneration Foundation Research Grants Program

The Macular Degeneration Foundation Research Grants Program, established in 2011 in the Foundation's tenth year, took on the challenge of providing up to $10 million for research on Macular Degeneration over the next ten years. To donate please call 1800 111 709 or go to www.mdfoundation.com.au

"In the past 18 years there have been great steps forward in diagnosis and treatment of Macular Degeneration. 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

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 and circumstances may 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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For further information and support, or a free MD information kit, call the MD Foundation's Helpline 1800 111 709 or visit www.mdfoundation.com.au

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