Macular Degeneration Foundation®

Our focus is your vision

Research Update December 2011

This update is a summary of some of the latest developments in Macular Degeneration research. This is an area of significant investment and effort, and some research projects are showing great promise. However, it takes many years to show that a new treatment is safe and effective before it can be approved (registered) and subsidised by the government.

Main areas of Macular Degeneration (MD) research

Identification of the causes of MD

MD is a complex disease and the reasons for it occurring are still not fully understood. The more that is known about what causes MD, the more options become possible for prevention and treatment.

Disease risk factors

Research which examines environmental and genetic risk factors helps determine who is more likely to have MD. This can lead to answers on which foods and treatments can slow the progression of the disease.

Diagnostic tests

Better diagnostic tests mean earlier and more accurate diagnosis of people at risk which can lead to earlier intervention.

Medical treatment

This includes drugs, drug implants, gene therapy and stem cell therapy. There are now at least 33 new medical treatments that are being tested in humans.

Surgical treatment

This can include laser, implantation of miniature telescopes and 'bionic eyes'.

Psycho-social and rehabilitation

Research can cover the management of psychological effects of vision loss such as grief and depression, the development and improved use of low vision aids, and ways to maintain quality of life and independence.

Medical research is difficult, risky, time consuming and very expensive.

The total time from initial identification of a potential drug ('discovery') until it is registered varies greatly but averages about 12 years.

For every 5,000 to 10,000 potential drugs that are tested during the discovery phase, about 250 progress to pre-clinical testing, approximately 10 start human trials and only one is registered and available for use.

During this time, researchers look at issues such as how to manufacture the drug consistently, its stability under different conditions, how it is metabolised (broken down) by the body, how it actually works, whether it can cause cancers or birth defects, how it is managed by people with particular medical issues such as heart disease or kidney problems, the optimal dose, side effects, efficacy, interactions with other drugs and many other issues.

It has been estimated that it costs between $500 million and $1.2 billion to bring the typical new drug a point where it can be registered.

Drugs that are similar to ones already available will tend to be quicker and cheaper to develop, whereas totally new drugs will usually take longer and be more expensive.

Medical devices and new surgical treatments also move through these phases, although time lines can be much shorter.

Medical Research Phases

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

Research phase	Patients studied	What studied	Average duration
Discovery	Usually laboratory work	What causes the disease, identify targets (eg 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	1000 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 (after registration)	Consenting patients using the test treatment once launched	Long term monitoring of safety and efficacy after drug is launched	Ongoing

The Research Process

A good example of the research process is from scientists at the University of Kentucky who reported in 2011 that levels of an enzyme called DICER1 were low in people with dry MD. This finding could potentially produce an early warning test for people at risk of developing end-stage dry MD ('geographic atrophy'). To test this theory, they selectively bred mice which had low DICER1 levels. All of these mice developed degeneration of the macula.

The researchers then found that low DICER1 levels caused a build-up of a toxic RNA molecule in the retina which then caused degeneration of the tissue. They are now developing a drug which can block this toxic RNA molecule. It has already been tested in human retina cells grown in a test tube, showing good effect. Human subjects will now be tested.

It has taken many years to get to this stage, and many more will be needed to fully develop and test the drug before it can be registered for general use. This process is typical of how new drugs are developed.

What causes MD?

MD is a complex disease and is influenced by several factors:

1. **Genetics and inflammation.** Mutations in one or more of at least 12 genes have been shown to have a role in at least 70% of MD cases. Most of these mutations involve a part of the immune system known as 'complement' and reduce one's ability to fight inflammation of the retina.

2. **Oxidative damage.** The eye is a very active organ, requiring significant energy and producing large amounts of waste products. These waste products are normally removed from the eye, but in some people, waste products remain, causing oxidative damage. Certain foods and supplements (anti-oxidants) or drugs help reduce this damage.

3. **Response to injury or tissue damage.** An organ or tissue normally responds to damage by trying to heal. This response may actually make things worse. In wet MD, the new, leaky blood vessels that form may be an example of the retina trying to heal itself in a process that has gone wrong.

Types of treatment

Treatments can be broadly grouped into two main categories:

1. Where some macular function still remains, treatments aim to prolong or improve the function of remaining vision, e.g. nutrition, drugs , gene therapy, or laser.

2. When all or most central photoreceptors (light sensitive cells) are dead, treatments aim to replace the dead cells or simulate vision, e.g., stem cell treatment, the artificial retina or 'bionic eyes'.

Nutrition

It has been known for some years that an eye health diet which includes fish 2 to 3 times a week, leafy green vegetables, brightly coloured fruit and vegetables and some nuts can help reduce the risk of MD and also slow down disease progression.

There is also now good evidence that people who have a higher proportion of low glycemic index ("low GI") carbohydrates in their diet, rather than high GI carbohydrates, are at a lower risk of MD. Low GI carbohydrates tend to break down more slowly, and produce much smaller fluctuations in blood glucose levels. The good, low GI carbohydrates include most fruits and vegetables, sourdough or wholegrain breads (e.g., multigrain), rolled oats (porridge), and unprocessed barley and bran.

Supplements

It is now generally considered to be standard practice that patients with moderate to advanced AMD take a supplement conforming to the AREDS formula (zinc 80 mg, vitamin C 500 mg, vitamin E 400 IU, copper 2 mg per day), as this can reduce the risk of progression of MD by 20 to 25%. At this time, the only supplement that has good evidence of benefit for people with established MD is the AREDS formula.

The next generation of supplement is being studied in the AREDS2 trial. This study evaluates the effect of lutein, zeaxanthin and/or omega-3 supplements in addition to the removal of beta-carotene (high levels of which are known to be harmful to smokers) and the effect of lowering the zinc dose. The results of the AREDS2 study will not be available until the end of 2013.

Treatments for wet MD

Background

At the time of publication of this update, Lucentis (ranibizumab) is the most effective registered treatment for the management of wet AMD. It is reimbursed via the PBS for patients with wet AMD, providing certain medical criteria are met. Lucentis is an anti-VEGF drug which stops or slows the formation of the new blood vessels under the macula. In situations where Lucentis

is not reimbursed, Avastin (bevacizumab) is sometimes used. The use of Avastin in the eye is considered "off-label" as it has not been approved by the Therapeutic Goods Administration (TGA) for this particular use.

Trials involving Lucentis® and Avastin®

There are nine large trials underway directly comparing the safety and efficacy of Lucentis and Avastin for wet AMD.

The largest is the CATT study, which is being conducted by the National Eye Institute in the US, and involves 1200 wet AMD patients. The initial 12 month results were reported in mid-2011. This showed that Avastin results in similar visual outcomes to Lucentis after 12 months, although it is not quite as effective as Lucentis in restoring the retina to its normal thickness. Whether this is important will become evident when the 24 month results are released in 2012.

Unfortunately the CATT study was not large enough to adequately compare the safety of the two drugs. There are some concerns that relatively rare, but serious side effects may be more common with Avastin. More research is needed to clarify the longer term safety and efficacy of Avastin.

Eight similar, smaller studies, are currently running; results for these should be known between 2012 and 2014.

With the remarkable success of the anti-VEGF drugs such as Lucentis in the treatment of wet AMD, these drugs have now also been studied in other retinal conditions where new blood vessel formation and excess fluid (edema) is also a problem. As a result, Lucentis has recently been registered in Australia to treat macular edema related to diabetes and vein occlusions.

VEGF Trap-Eye (Eylea®)

The next drug which is likely to be registered in Australia for the management of wet MD is called Eylea. At the time of this update going to press, Eylea is being evaluated for use in Australia by the TGA. The precise date it will be available in Australia is not yet known as this depends on registration and subsequent reimbursement negotiations between the manufacturer and the federal government.

Eylea is given by an injection into the eye. The recommended dosing schedule is one injection per month for three months and then every second month. In two very large studies, 95% of patients with wet MD maintained vision over 12 months (defined as losing no more than 3 lines on the eye chart). These results are almost identical to those when Lucentis is given every month. A longer dosing interval in the second year is also being studied for Eylea. Its safety profile is very similar to Lucentis.

Pazopanib

This agent is given as an eye drop and appears to reduce the production of multiple growth factors (proteins) which cause the growth of new blood vessels in wet MD. A phase II study is comparing different doses of pazopanib, with Lucentis given when needed, versus regular Lucentis injections alone. If successful, this agent could reduce the number of injections of Lucentis needed. This study is due for completion in June 2012. An tablet version of pazopanib is now also being evaluated in a small pilot study.

E10030

This agent is given as an injection into the eye for wet MD (like Lucentis), but works on a different growth factor. It would be given in conjunction to Lucentis (or similar) injections, producing a larger effect than Lucentis on its own. A small phase I study showed that 60% of patients receiving the combination showed improved vision, compared to 33 to 40% of patients receiving Lucentis alone. Almost all other patients showed stabilisation of vision. It is now undergoing phase II studies.

AL32324

This drug, given as an injection in the eye has just completed a small phase II safety and efficacy study using different doses, with comparison to

Lucentis. Results are not yet available, although pre-clinical studies in mice showed significant reduction of new vessel formation.

Radiation treatment

The use of anti-VEGF injections combined with tiny doses of strontium x-ray delivered direct to the leaky blood vessels shows promise. Two techniques have been developed to deliver the x-ray without causing damage to nearby retinal cells. One technique is epimacular brachytherapy. A tiny probe is inserted in the eye to place the x-ray directly over the leaking blood vessels. A large study is evaluating if this technique will allow the number of Lucentis injections to be reduced to only 2 over 12 months.

The other technique, called I-Ray, uses a device to aim the x-ray beam right onto the leaking vessels. This technique has the benefit that it can be done without surgery, in the doctor's office. A large study is evaluating the safety and efficacy of this approach.

Neither x-ray technique is currently available in Australia.

Treatments for dry MD

At the moment, lifestyle modifications such as stopping smoking and dietary improvements are the only way to slow the progression of dry AMD. There is currently no proven treatment available for drusen or dry AMD.

Dry MD may be a uniquely human disease. As there are no known equivalent diseases in animals, early testing of potential treatments is much more difficult. Research strategies can be grouped into three main categories:

- drugs to promote survival of the photoreceptors and retinal pigment epithelium (RPE) in the retina
- drugs to prevent injury from oxidative damage and loss of nutrition to the eye
- drugs to suppress inflammation.

AL8309B (Tandospirone)

This is one of the most advanced projects for dry MD, currently in a phase III trial known as GATE, and is due for completion in February 2012. This drug is given as an eye drop, and works by protecting the retina from oxidative damage due to certain wavelengths of light. This study measures the reduction in scarring from the end stage of dry MD.

NT-501 (Ciliary Neurotrophic Factor)

This drug helps prevent the degeneration of retinal photoreceptors and is slowly released from a tiny capsule which is implanted inside the eye. The 12 month results of a phase 2 pilot study were published in 2011. Higher doses of NT-501 reduced the loss of photoreceptor cells and partly stabilised vision loss . Unfortunately, there was little effect on the scarring that occurs within the retinal pigment epithelium, lying under the photoreceptors. Larger studies are needed to see if this drug has a meaningful effect.

Brimonidine

This drug is already available in an eye drop as a safe and effective treatment for glaucoma. When it is given as a prolonged-release implant, it appears to protect the retinal photoreceptors from light damage. A phase 2 study was recently commenced, but results are not yet available.

Copaxone (glatiramer acetate)

While there is no direct connection between MD, Alzheimer's Disease and Multiple Sclerosis, they do have common elements including inflammation and the formation of deposits. In Alzheimer's, the deposits are plaque in the brain; in MD, the deposits are drusen in the retina. Copaxone is being investigated as a treatment for all three diseases. It is already being used to treat multiple sclerosis and has been shown to be safe when used for this condition.

An initial study showed that eyes treated with Copaxone had a reduction in drusen area of over 53% after 12 weeks. This is compared to patients without treatment whose eyes showed

an average 25% increase in the total area of drusen over 6 months. Longer trials with more patients are now needed.

ACU4429

This agent has demonstrated efficacy in several pre-clinical studies. It is given as a tablet and slows down the activity and waste production of rod (low light) photoreceptors in the outer retina, well away from the macula. It is believed that this will slow down the build-up of toxic waste under the retina, which in turn will slow down the formation of drusen. A phase 2 trial is planned in the US to evaluate safety and efficacy in patients with dry AMD and geographic atrophy.

Fenretinide

Fenretinide is a synthetic modification of Vitamin A, taken orally, which appears to have three important mechanisms on the development of both dry and wet AMD:

- it reduces some of the toxins which accumulate on the macula, leading to the formation of drusen
- it has anti-inflammatory properties
- it may inhibit the formation of abnormal blood vessels.

Fenretinide has been investigated as a potential treatment for many other diseases, and has a proven safety profile from over 30 large studies. It is well tolerated, although many patients have trouble seeing at night.

Results from a major phase 2 trial in the US were announced in October 2010, and showed that fenretinide can slow down the formation dry MD scarring and also reduce the rate of progression to wet AMD by more than 50%.

Unfortunately, due to some complex regulatory issues, this study may need to be repeated before it can move to later phase studies. The project is currently on hold pending discussions with the US regulatory agency and financiers.

2RT laser

Initial results with this new type of ultrashort, low energy laser, which does not destroy retinal cells, have been promising. This Australian development has been shown to be effective in removing drusen in people with the early stages of dry MD. The 12 month results from 24 patients in Melbourne have just been presented. Two-thirds of these patients showed an improvement in visual acuity and a reduction in the number and area of drusen on the macula. The 12 month results in 50 patients will be available shortly. Currently, there is no evidence that removing drusen with laser leads to a long-term reduction in the risk of developing end-stage disease. Preparation is therefore now underway to start a large, long-term, multi-centre study to see if the removal of drusen will indeed have an impact on the rate of progression from early to late stage MD.

Gene therapy (Wet and dry MD)

Gene therapy possibly represents the most likely approach for an eventual cure for MD as this could potentially 'fix' the faulty gene or genes that are involved in 70% of MD cases.

A major advance with gene therapy for MD occurred in 2011 when the first human trials started, using a treatment called RetinoStat. Genes that stimulate the production of a protein that inactivates the VEGF molecule are delivered to the eye by piggy-backing on a harmless viral 'vector'. Initial animal studies have been very promising.

Other types of gene therapy in which defective genes involved in the 'complement' immune response are replaced with functional genes are also under development, and are likely to have a significant impact on dry MD. A key benefit of gene therapy is that a single injection could potentially provide treatment for many years, possibly even for life.

Stem cell research

Please note: The Foundation recognises and respects different points of view concerning stem cell research. The Foundation's role is simply to report on key research for your information.

What are stem cells?

Stem cells are very special types of cells that are able to change into specialised tissue or organs, such as retinal tissue.

Stem cells come from two main sources:

1. Cultures of cells taken from the very early stage of embryo development at about day 4 to 5. These are usually from surplus or unviable embryos that have been created in IVF clinics. These cells are considered the most adaptable type of stem cell.

2. 'Somatic' or adult stem cells which are obtained from either umbilical cord blood, or from certain tissues in children or adults. These cells are generally more difficult to 'coax' into the type of tissue that is needed.

The goal of stem cell research is to develop functional new retinal tissue to replace damaged or dead tissue. The ultimate aim is to restore some functional vision in people who have lost most or all of their central vision. If successful, it is likely that a single implantation of stem cells will last for several years and potentially a lifetime.

Along with ethical issues being discussed and debated, other issues associated with stem cell implantation include the potential for rejection and ensuring that the cells do not change into other types of tissue, including tumours.

Human Embryonic Stem Cells (hESCs)

After very successful animal studies that have demonstrated formation of good, stable retinal pigmented epithelial cells, a US company started phase 1/2 human trials with transplanted human embryonic stem cells (hESCs) in the US and Europe in 2011. This is one of the first areas where hESCs have been transplanted in humans.

Trials are underway to assess the safety of hESCs in people with Stargardt's Disease (a form of MD that affects young people) and in age-related MD. In September 2011, the first few patients showed no safety issues and higher doses of cells are now being implanted. Information on whether vision improves is not yet available.

Several other projects using hESCs are progressing and some (eg the London Eye Project) are due to commence human studies in 2012.

'Adult' Stem Cells

hUTC cells

A phase 1/2 study has started in the USA, using human umbilical tissue-derived cells (hUTCs). In phase 1, the patients in the trial will be legally blind due to end stage dry AMD. The first outcome being tested is the safety of treatment. In phase 2, safety and vision outcomes will be tested. In time, patients with better vision will also be studied.

University of Nebraska

At the end of 2010, researchers from Nebraska USA found that a certain type of retinal cell called a Muller cell, could act as an adult stem cell to produce retinal tissue. The adult stem cell research has been performed on rats and mice and involved the activation of adult stem cells using a combination of small proteins called peptides. Some of the activated cells moved to the location of the dying retinal cells and then changed into retina-like cells, with a significant improvement in light perception. If this work can be duplicated in humans, it will help overcome the concerns of some people about the use of stem cells from other sources including embryos.

Similar work is taking place at the University of Georgetown and other locations.

Other treatments

Implantable telescope

The Implantable Miniature Telescope (IMT) is now available in the US but has not yet been registered in Australia. The telescope is implanted into the eye in the same position that an intraocular lens would be placed after a cataract extraction (patients in the study have their existing lens or lens implant removed). The telescope enlarges images up to three times, but only in the centre. While the implant has helped some people, its use requires careful patient selection and extensive training. The peripheral vision of the eye in which the IMT is placed is unfortunately eliminated.

Artificial retina and 'bionic eyes'

Several types of retinal implants and bionic eyes are under development, and one ('Second Sight') is already available in Europe for people with black or total blindness. Two projects are underway in Australia. It is important to recognise that the initial versions of these products can only produce the most basic of images, and will only be suitable for people who are black blind. (People with MD do not become black blind.)

It is hoped that with further development, these devices may eventually be of use for people with central vision loss from MD.

Treatments with inadequate scientific evidence

Promotion of treatments for MD that have not been adequately tested for safety or efficacy often appears in the media.

These treatments are often promoted with extravagant claims and "compelling patient testimonials".

Proper evidence to support these treatments is typically unavailable.

If you are uncertain about the legitimacy of any treatment, we strongly advise that you first speak to your ophthalmologist or call the Foundation on 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.

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, please call the Foundation's helpline on 1800 111 709 or visit www.mdfoundation.com.au

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