

# Are There Any Viable Treatments For Age Related Macular Degeneration?

Michael Radparvar

Michael Radparvar will graduate in January 2020 with a Bachelor of Science degree in Biology.

## Abstract

*Stem cells seem to offer an alternative venue for treating many cell related diseases, such as age-related macular degeneration (ARMD). ARMD is a progressive neurodegenerative medical condition, which primarily affects the retinal pigmented epithelium (RPE), resulting in degeneration of photoreceptors. Scientists have been successful in implanting stem cells into the eyes of rats. These injected cells sustained visual function and photoreceptor integrity without any cancerous cell formation. There are numerous treatments available to slow down the progression of ARMD. Depending on the type of ARMD, doctors may either recommend leading a healthier lifestyle or that one should undergo surgery. Numerous risk factors can increase one's chances of getting ARMD depending on one's age and race. Bad habits, such as cigarette smoking, can contribute to the progression of ARMD. It is important to get a comprehensive dilated eye exam periodically. Many eye diseases that don't have any warning signs can be detected with such an eye exam.*

## Introduction

The most versatile cell types in the human body are embryonic stem cells. Stem cells have three unique general properties that distinguish them from other cells in the body. One is that these cells can replicate themselves even after long periods of inactivity. Secondly, stem cells are unspecialized. These cells are not programmed to become any specific tissue. For example, stem cells can't work with other red blood cells to carry oxygen containing molecules through the blood stream. Thirdly, under certain physiologic or experimental conditions, stem cells can become the specialized cells that make up tissues and organs (National Institutes of Health 2016).

When stem cells divide, they can make either more stem cells, or can differentiate into a specialized cell which is tasked with a specific function. For example, these stem cells can turn into motoneurons which are used for motor skill or into cardiomyocytes to help pump blood through the arteries. However, Adult stem cells can only generate cells that are like the tissue in which they are located in (Tuch, 2006). For example, hematopoietic stem cells in the bone marrow form only cells that give rise to the different types of blood cells and cannot make nerve cells for the brain.

Embryonic stem cells are made from oocytes that have been fertilized in vitro and not in a woman's body. The process of priming the cells in an in vitro fertilization clinic is known as cell culture. Human embryonic stem cells are primed by placing an embryo into a culture dish that contains a culture medium. With the right physiological conditions, these cells begin to divide and spread over the surface of the dish forming millions of unspecialized stem cells. Although scientists have not agreed upon a battery of tests to ensure they are growing only unspecialized cells, there are some common tests performed to determine the cells fundamental properties. One technique used is by looking for particular cell surface markers, such as transcription factors, that are generally produced by undifferentiated cells.

Stem cells in their culture dish can remain undifferentiated as long as they are under the appropriate conditions. However, cells automatically begin to differentiate once they are allowed to cluster together to form embryoid bodies. These cells can then begin to form tissue specific cells, such as muscle or nerve

cells. Although differentiation is a sign of a healthy culture, this process is generally uncontrolled, and therefore an inefficient way to produce specialized cells. In order to create a more controlled experiment, scientists change around the chemical composition of the culture medium or by inserting specific genes to specialize the cells in an organized fashion.

Human embryonic stem cells have many applications in clinical use and in research. One useful application is in cell-based therapies, situations where stem cells are induced to turn into specialized cells. Through this process, new cells which are needed to repair destroyed tissue can be formed. For example, these specialized cells can replace bone marrow, muscle, and brain cells that are injured or malfunctioning. These cells form an internal repair system by cell mitosis for as long as the organism is alive. Due to their ability to replace damaged cells, stem cells seem to offer an alternative venue for treating many cell related diseases as well. If scientists can reliably find a way to differentiate the cells in an organized manner, then they may be able to cure many diseases in the future (Weiss, Troyer, 2006).

One of the diseases that scientists believe embryonic stem cells can treat is age related macular degeneration (ARMD) (Shroff, 2015). Over 10 million Americans have vision loss related to Macular degeneration. Macular degeneration is the third most common pathological condition leading to vision impairment (Resnikoff, et. al., 2004). ARMD is a progressive neurodegenerative medical condition, which primarily affects the retinal pigmented epithelium (RPE), resulting in degeneration of photoreceptors. This causes loss of vision in the center of the field of vision. The disease is caused by the deterioration of the macula, a region that is located at the center of the retina and is responsible for focusing central vision in the eye. This allows people to ride their bike or recognize a familiar face. Common symptoms include not being able to see in dim light, seeing spots, and distorted vision.

There are two types of ARMD. There is the wet as well as the dry form. Most of the cases of ARMD are the dry form. Dry ARMD is also known as non-neovascular ARMD as well as non-exudative ARMD since there are no fluids that leak into the macula from blood vessels. Although people with this form of ARMD may have fair central vision of at least 20/40, they

## Michael Radparvar

may have other functional limitations, such as fluctuating vision, poor night vision, and pixelated vision. In this form of ARMD, the deterioration by the macula is linked with the appearance of drusen. Drusen are small yellow deposits that form under the macula. These deposits are buildups of shapeless acellular debris from the basement membrane of the RPE. This buildup of drusen causes the macula to thin and dry out, thereby causing the macula to lose its function. This process is known as atrophy. The amount of vision loss that occurs is directly proportional to the amount as well as the location of the drusen. Advanced cases of dry ARMD are also known as geographic atrophy (GA) since large areas of the retina stop functioning. Patients with GA usually see large blank spots in their central vision because their macula has deteriorated. Usually, most people over 50 years old have a drusen buildup in at least one of their eyes. Currently, there is no known cure for this form of the disease.

However, some cases of dry ARMD progress into the wet form. In the wet form, there is an abnormal blood vessel growth under the macula. This type of growth is known as choroidal neovascularization (CNV). Once CNV has occurred in one eye, the patient has a higher risk that the other eye will get CNV as well. These new blood vessels are generally weak and can rupture easily. When they rupture, they leak fluids, such as blood and lipid containing solutions. This causes the macula to bulge, thereby causing a distorted central vision. These conditions can cause severe vision loss in a short amount of time. In this form of ARMD, patients may see spots because of the fluid buildup under the macula. Therefore, periodic eye exams are vital, especially if the patient is at a higher risk of contracting ARMD.

There are three stages in ARMD. There is early, intermediate, and late stage ARMD. During early stage, most people don't realize any of the symptoms. Therefore, it is crucial to have regular eye exams. Early ARMD is diagnosed by the appearance of drusen the size of 63 microns by the macula. In the intermediate ARMD, there may be some vision blur in the central vision and by late ARMD there is a noticeable vision loss in the central vision.

Medical experts aren't exactly sure what causes ARMD but once present, many factors contribute to its progression. A person's age is by far the biggest factor for ARMD. Once one turns 50, they should visit an optometrist for a comprehensive dilated eye exam. Many eye diseases that don't have any warning signs can be detected with such an eye exam. This exam includes a visual acuity test, a visual field test, dilation, and tonometry. Annual exams are recommended once a year once one turns 60. However, if one is African American, then they should get one when they turn 40 since they have a higher risk for glaucoma. Although there aren't any cures presently available, there are numerous treatments for ARMD. Many doctors may prescribe a strict diet and exercise to slow down the progression. However, none of them can cure the disease, except potentially stem cells.

Although stem cells may offer new therapies, their use has

been very controversial. People oppose stem cell research since one is harvesting a fertilized egg. They believe that this is wrong since this is tantamount to killing an unborn child, and therefore one should respect the value of a human life. However, others feel that morally it's our duty to prevent or alleviate a person from suffering.

### Methods

Literature for this article was obtained primarily using Touro College's Online library. Other databases, such as PubMed, were used. Additionally, Google Scholar was valuable for finding necessary and relevant articles.

### Discussion

The retina of the eye is tasked with converting light into vision. At the center of the retina is the macula. In the retina, there are the rods and cones which process light into nerve impulses. Behind the photoreceptor layer is the retinal pigmented epithelium (RPE). The RPE is tasked with delivering nutrients and removing wastes from the photoreceptor cells. In ARMD, RPE stops functioning, causing the cones and rods to deteriorate. Today, scientists are using stem cell research to understand how diverse cells in the retina interact with one another. This has led to discovering new ways of replacing photoreceptors and the underlying RPE.

Generally, replacing dead cells with stem cells is very challenging since the stem cells would have to establish new connections with the surrounding nerve fibers that ultimately relay the message to the brain. However, the eye is a great target for stem cell research since there are many barriers in the eye, such as tight cell junctions, therefore making it relatively self-contained. This prevents the migration of cells outside of the eye. Furthermore, with the use of an ophthalmoscope it is easy to assess the effectiveness of the treatments. Doctors can also compare the treated eye with the other eye to evaluate the effectiveness of the treatments.

RPE cells are easier to integrate with existing retinal cells since they don't need to connect with nerve fibers. With stem cells research, one can use new RPE cells to replace dead RPE cells. If the stem cells are replaced before the photoreceptors have completely deteriorated, then the new RPE cells may be able to prevent existing photoreceptors from dying, thereby preventing the progression of the disease. Stem cells can also be used to discover new therapies. When damaged RPE cells are stressed, they produce characteristics of ARMD. These damaged cells can then be studied to evaluate the different surface markers present which can help in early intervention and in getting a better diagnosis.

Scientists have come up with different methods to replace the RPE layer. One method is using human embryonic stem cells. These cells are naturally pluripotent when harvested and can renew for long periods if properly maintained in vitro. They can

## Are There Any Viable Treatments For Age Related Macular Degeneration?

transform into the ectoderm, endoderm, and mesoderm. These three primary germ layers can differentiate into all the cells in the body. However, there are numerous obstacles raised with this method. One of the problems is whether it is ethical to harvest embryos since they can turn into a fetus (Narsinh, et. al., 2011). Another challenge that must be overcome is the limited supply of human embryo donors.

Another method researchers have used is induced pluripotent stem cells

(hiPSCs). These are usually epithelial cells that are reprogrammed to behave like embryonic stem cells. They can then be used to grow rods and cones or RPE cells. The landmark discovery of hiPSCs has been hailed as a significant advance in stem cell research. This method circumvents the ethical debate with embryonic stem cells since no human embryo is destroyed ex utero. However, there are numerous problems with this method as well. Extensive research has shown that these cultured cells can turn into benign or malignant tumors (Ho, et. al., 2012). Therefore, these issues preclude clinical use of these cells for now.

Another method which scientists are experimenting with is adult stem cells. This method entails growing RPE specific stem cells from adult stem cells. One source for such cells is from eyes donated to eye banks. These cells are less likely to be rejected if used in implants. However, there usually is a limited amount in each tissue, therefore making it harder to find and purify. Furthermore, these cells can't be stored for any length of time before they turn cancerous (Reya, et. al., 2001).

### Delivery Method for Stem Cells

Although there are no FDA approved cures for ARMD, implantation of healthy RPE into the macula may prove to be an effective treatment. The following procedure was used to deliver RPE into rats. After the rat was put under a general anesthetic, a hole was created in the eye using a sharp needle. Then, a blunt needle was inserted into the hole until it reached the RPE layer, into which the stem cells were injected (Westenskow, et. al., 2015).

In one study, animal models, such as rats and mice with macular degeneration, were treated with stem cells that become RPE cells (Lu, et. al., 2009). To simulate real life conditions, the rats were under a 12-hour light /dark cycle. One day prior to their transplantation, all animals in the main experiment were administered cyclosporine to prevent organ rejection. Before the researchers administered the cells, they washed the cells in balance salt solution. Two weeks after the transplantation, the rats received an intraperitoneal injection of dexamethasone. This steroid was injected to treat the resulting inflammation.

These injected cells sustained visual function and photoreceptor integrity without any cancerous cell formation. Visual acuity increased when the models received a dose between 5000-100,000 RPE cells. Following the procedure, the rats were

monitored to check for any adverse reaction. They found that visual function was sustained for at least two months. The cells themselves survived for at least half a year before they started to deteriorate. However, this deterioration in visual acuity can be due to insufficient cyclosporine. Another hypothesis of why the cells deteriorated can be because the transplantation may need to be repeated several times in order to sustain their therapeutic effect.

### ARMD Treatments

For early dry ARMD, doctors recommend a diet that is high in antioxidants, such as strawberries and oranges. However, if the patient has an advanced stage of dry ARMD, such as GA, then the doctor may prescribe supplements that increase vital vitamins that support the cell.

Until recently, the only treatment for wet ARMD was laser photocoagulation. This treatment by an ophthalmologist is a minimally invasive procedure which uses a laser to burn and destroy leaking blood vessels. However, this treatment cannot restore vision that has been lost already. One drawback to their use is that most CNV lesions are too big to be treated by laser coagulation. Another is that there is a high chance that the leakage will reoccur over time. Because of these limitations, scientists have been looking for alternative therapies that are safe and effective for a long period of time.

One alternative treatment that is widely used today is Anti-vascular endothelial growth factor (VEGF) therapy. This therapy includes periodic intraocular injections of a chemical called anti-VEGF. Normally, VEGF is beneficial for the circulatory system since it helps promote the growth of new blood vessels. However, having too much by the macula can have deleterious effects on it since they promote the growth of weak new blood vessels. This intravitreal shot of anti VEGF stops the development of new blood vessels by the macula, thereby preventing any further leaks. However, there are numerous side effects with this treatment. Patients have complained about vitreous floaters. This happens since the doctor punctures the vitreous layer of the eye. Another side effect observed was an elevated eye pressure. This can cause glaucoma if left untreated.

### Human Implant

Although stem cells have been proposed as a potential treatment in treating ARMD, there are still numerous drawbacks to their use. Safety concerns have been raised since there is a risk that these cells may turn into unwanted cell types which can lead to tumor formation in the eye and potential immune rejection. Although stem cells were discovered in the late 1990s, scientists did not know how to find a safe way of implanting them. The first reported transplanted hESC-derived cells into the macula was in 2012. hESC-derived retinal pigment epithelium cells were transplanted into the subretinal portion of the of the eyes of

## Michael Radparvar

dry ARMD patients (Schwartz, et. al., 2012). Ninety-nine percent of the stem cells differentiated into RPE cells. These differentiated cells integrated into the host forming a homogenous RPE layer. Post-surgery, structural evidence showed that the cells had attached and continued to persist during the study. During the first four months, there were no signs of hyperproliferation, cell rejection, or abnormal growth.

The scientists didn't find any signs of adverse proliferation or any other type of ocular disease. This method proved to be a safer method for treating ARMD than other conventional methods, such as vitreoretinal surgery and immunosuppression. The results of this study provide the first evidence for medium to long term safety as well as graft efficacy. These results suggest that stem cells can be a safe alternative for many medical diseases that require tissue replacement. Therapeutic goals for the future will be to treat the patient in the earlier stages of macular degeneration, thereby preventing the photoreceptors from decaying.

### Risk Factor

A study was conducted to evaluate the effects of antioxidants on ARMD. In this clinical experiment, they enrolled 3,640 participants who showed signs of ARMD. These participants had drusen buildup in at least one of their retinas. The size of drusen buildup was between 63-150 microns. Participants were randomly assigned supplements that contained either 500 mg L-ascorbic acid, 400 IU tocopherols, or a placebo. The researchers found that compared to the placebo a high dose of L-ascorbic acid and various tocopherols may delay the progression of ARMD and other forms of vision loss. These supplements showed no adverse effects, proving their safety (Age-Related Eye Disease Study Research Group, 2001).

A study was conducted to assess the risk of smoking in men. This study consisted of 21,157 US male physicians who did not have any known diagnosis of ARMD. Of them, 11% were current smokers, 39% were past smokers, and 50% that never smoked. Over the course of 12 years, they found 268 incidents of ARMD. Current smokers who smoked a pack a day had a 240 percent risk increase compared to nonsmokers. Past smokers had a 30 percent increased risk of contracting ARMD. Current smokers who smoke less than 20 cigarettes had only a modest risk increase of 26 percent (Christen, et. al., 1996). Unlike other risk factors, such as age, smoking is an avoidable risk factor.

Since there aren't any cures that are reliable for ARMD, it is therefore recommended to avoid smoking altogether. However, it could be that the study on smoking isn't 100 percent accurate. It could be that the subjects who didn't smoke had a slower progression since they ate foods rich in omega-3 fatty acid. This acid can be found in many common household products, such as fish and canola oil. In a study conducted with 681 twins, they found that having 2 or more servings of fish reduced the risk of ARMD by 45 percent (Seddon, et. al., 2006).

Although some fruits and vegetables can slow down the progression of ARMD, such as those rich in L-ascorbic acid and tocopherols, other vegetables can be bad for ARMD. One study tried to find out if dietary nitrates can increase your chance of getting ARMD. These nitrates can be found in leafy vegetables, such as lettuce and spinach. In this study, there were 2,856 participants. The scientists took numerous potential cofounders into account such as age, sex, smoking, energy intake, and fish consumption. The participants were monitored for 15 years. The scientists found that those who had a dietary nitrate intake had a 39 percent increase incidence of having ARMD (Gopinath, et. al., 2018). However, this percentage increase cannot be said to apply for all ethnic groups.

A prospective cohort study of 6,176 participants between the ages of 45 to 85 was used to find the prevalence of ARMD between four racial groups. These groups were white, black, Hispanic, and Chinese. The method they used to test for ARMD was by taking a picture of the fundus through the dark-adapted pupils, whereupon they were able to measure the drusen size. What they found is that Hispanics had a 1.8 percent increase in prevalence compared to the black ethnic group. The Chinese had a 2.2 percent increase, and the white had a 3 percent increase compared to the blacks. Differences in age, gender, pupil size, body mass index, smoking, alcohol drinking history, diabetes, and hypertension status did not explain the variability among the 4 racial/ethnic groups (Klein, et. al., 2006).

A person's age is by far the biggest factor for ARMD. In a population-based study, scientists tried to find the prevalence of ARMD in a sample of Hispanic individuals over the age of 50. All 4,774 participants had an initial ophthalmic evaluation to determine a baseline for comparison. Over the course of the study, the scientists monitored drusen size, drusen type, and the area covered by drusen. They found that the prevalence of early and late ARMD increased with age. The prevalence of early ARMD varied with age as follows: people between 50 and 60 had a 20 percent increase, while those aged 80 and older had a 54 percent increase. The prevalence of late ARMD varied with age as well. Those in the age group of 50 to 60 had a .1 percent increase, while those 80 years and older had a 4.3 percent increase (Muñoz, et. al., 2005).

### Conclusion

Currently, there is no FDA approved cure for ARMD. However, one promising cure currently being researched is stem cell transplantation. However, there are numerous obstacles that still need to be overcome before they can be safely implanted into patients. Depending on the type of ARMD, doctors may either recommend leading a healthier lifestyle or that one should undergo surgery. As one ages, one is more prone to getting ARMD. Therefore, it is important to get a comprehensive dilated eye exam periodically.

## Are There Any Viable Treatments For Age Related Macular Degeneration?

### References

- Age-Related Eye Disease Study, Research Group. (2001). A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and... *Archives of Ophthalmology*, 119(10), 1417-36. Retrieved from <https://search.proquest.com/docview/231954375?accountid=14375>
- Christen WG, Glynn RJ, Manson JE, et al. A prospective study of cigarette smoking and risk of age-related macular degeneration in men. *JAMA: Journal of the American Medical Association*. 1996;276(14):1147-1151. <https://erms.tourolib.org/url/http://search.ebscohost.com/login.aspx?direct=true&db=ccm&AN=107268789&site=ehost-live>. Accessed December 25, 2018.
- Gopinath B, Liew G, Kifley A, et al. Association of Dietary Nitrate Intake with the 15-Year Incidence of Age-Related Macular Degeneration. *Journal of the Academy of Nutrition & Dietetics*. 2018;118(12):2311-2314
- Ho P-J, Yen M-L, Yen S-F, Yen BL. Current Applications of Human Pluripotent Stem Cells: Possibilities and Challenges. *Cell Transplantation*. 2012;21(5):801-814. doi:10.3727/096368911x627507.
- Klein R, Klein BEK, Knudtson MD, et al. Prevalence of Age-Related Macular Degeneration in 4 Racial/Ethnic Groups in the Multi-ethnic Study of Atherosclerosis. *Ophthalmology*. 2006;113(3):373-380. doi:10.1016/j.ophtha.2005.12.013.
- Lu B, Malcuit C, Wang S, et al. Long-Term Safety and Function of RPE from Human Embryonic Stem Cells in Preclinical Models of Macular Degeneration. *Stem Cells*. 2009;27(9):2126-2135. doi:10.1002/stem.149.
- Muñoz, B., Klein, R., Rodriguez, J., Snyder, R., & West, S. K. (2005). Prevalence of age-related macular degeneration in a population-based sample of hispanic people in arizona: Proyecto VER. *Archives of Ophthalmology*, 123(11), 1575-80. Retrieved from <https://search.proquest.com/docview/231967184?accountid=14375>
- Narsinh KH, Plews J, Wu JC. Comparison of human induced pluripotent and embryonic stem cells: fraternal or identical twins?. *Mol Ther*. 2011;19(4):635-8.
- National Institutes of Health. Stem Cell Information., U.S. Department of Health and Human Services Bethesda, MD. Available at: <http://www.stemcells.nih.gov/info/basics/3.htm>. Accessed October 26, 2016
- Resnikoff S, Pascolini D, Etya'ale D, et al. Global data on visual impairment in the year 2002. *Bull World Health Organ*. 2004;82(11):844-51.
- Reya, T., Morrison, S. J., Clarke, M. F., & Weissman, I. L. (2001). Stem cells, cancer, and cancer stem cells. *Nature*, 414(6859), 105-111. doi:<http://dx.doi.org/10.1038/35102167>
- Schwartz SD, Hubschman J-P, Heilwell G, et al. Embryonic stem cell trials for macular degeneration: a preliminary report. *Lancet*. 2012;379(9817):713-720. doi:10.1016/S0140-6736(12)60028-2.
- Seddon JM, George S, Rosner B. Cigarette smoking, fish consumption, omega-3 fatty acid intake, and associations with age-related macular degeneration: the US Twin Study of Age-Related Macular Degeneration. *Archives Of Ophthalmology (Chicago, Ill: 1960)*. 2006;124(7):995-1001.
- Shroff G. (2015) Use of Human Embryonic Stem Cells in the Treatment of Age-Related Macular Degeneration. *J Clin Exp Ophthalmol* 6:446. doi: 10.4172/2155-9570.1000446
- Tuch, B. (2006). Stem cells - A clinical update. *Australian Family Physician*, 35(9), 719-21. Retrieved from <https://search.proquest.com/docview/216301343?accountid=14375>
- Weiss, M. L., & Troyer, D. L. (2006). Stem cells in the umbilical cord. *Stem Cell Reviews*, 2(2), 155-62. doi:<http://dx.doi.org/10.1007/s12015-006-0022-y>
- Westenskow PD, Kurihara T, Bravo S, et al. Performing subretinal injections in rodents to deliver retinal pigment epithelium cells in suspension. *J Vis Exp*. 2015;(95):52247. Published 2015 Jan 23. doi:10.3791/52247