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# Dry Age-Related Macular Degeneration Pharmacology

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## Abstract

Age-related macular degeneration (AMD), the most common form of irreversible blindness in the industrially developed world, can present years before a patient begins to lose vision. For most of these patients, AMD never progresses past its early stages to the advanced forms that are principally responsible for the vast majority of vision loss. Advanced AMD can manifest as either an advanced avascular form known as geographic atrophy (GA) marked by regional retinal pigment epithelium (RPE) cell death or as an advanced form known as neovascular AMD marked by the intrusion of fragile new blood vessels into the normally avascular retina. Physicians have several therapeutic interventions available to combat neovascular AMD, but GA has no approved effective therapies as of yet. In this chapter, we will discuss the current strategies for limiting dry AMD in patients. We will also discuss previous attempts at pharmacological intervention that were tested in a clinical setting and consider reasons why these putative therapeutics did not perform successfully in large-scale trials. Despite the number of unsuccessful past trials, new pharmacological interventions may succeed. These future therapies may aid millions of AMD patients worldwide.

### Keywords

Emixustat; GSK 933776; iPSC-derived RPE; Lampalizumab

## 1 Introduction

Age-related macular degeneration (AMD) is the most prevalent cause of blindness in the elderly in the USA (Schmier et al. 2012) and affects as many as one in eight individuals over the age of 80 (Zeng et al. 2016). AMD affects many different cell types, including the retinal pigment epithelium (RPE) (Ambati and Fowler 2012), choriocapillaris endothelial cells (ECs) (Zeng et al. 2016), and photoreceptor cells (Carr et al. 2013). Early AMD initially presents with drusen, whitish or yellowish punctate extracellular deposits >63 μm in diameter positioned between the RPE and Bruch's membrane (Ferris et al. 2013). Changes to RPE pigmentation mark the transition to intermediate AMD (Ratnapriya and Chew 2013). Noticeable declines in visual function do not occur until advanced forms of AMD, which may take years (Buschini et al. 2015). Advanced AMD takes two primary forms defined by whether neovascularization occurs; geographic atrophy (GA) (Buschini et al. 2015) presents

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with regional RPE cell death without blood vessel intrusion, while exudative (i.e., wet) AMD does (Wong et al. 2008). Over three-quarters of legal blindness results from wet AMD (Buschini et al. 2015), but GA accounts for the vast majority of advanced AMD cases (Tarallo et al. 2012). Unfortunately, no therapeutic options for dry AMD are available (Tarallo et al. 2012).

Because age is the greatest risk factor for AMD (Bora et al. 2014) and the US census data indicates the number of elderly individuals is expected to greatly increase in the next few decades, the number of patients with AMD is expected to almost double by the year 2050 (Rein et al. 2009). Given the large number of patients with untreatable dry AMD and the reduced quality of life experienced by these patients, there is an immediate need for effective medications to treat the disease. To date, no potential therapeutics show efficacy with respect to slowing or reversing dry AMD progression. The purpose of this chapter is to explore the different therapeutic targets and their proposed treatments and to consider reasons for why these approaches have not been effective.

## 2 Current Strategies for Addressing Dry AMD

Lifestyle modification and dietary supplements are the only options to combat AMD development, progression, and associated visual function decline. Modifiable risk factors for dry AMD include smoking and obesity (Cheung and Eaton 2013). Smoking in particular has been associated with development and progression of AMD (Buschini et al. 2015), and some evidence AMD risk has a dose-dependent relationship with smoking (Velilla et al. 2013). Analysis of pooled datasets from the Beaver Dam Eye Study (Klein et al. 1993), Rotterdam Study (Vingerling et al. 1995), and Blue Mountains Eye Study (Mitchell et al. 1995) suggests smokers have an approximately three-fold greater risk of AMD than patients who never smoked (Smith et al. 2001). Patients who quit smoking greatly reduce their risk for developing AMD, but are still at a greater risk for AMD than patients who never smoked (Velilla et al. 2013; Smith et al. 2001). Much of the RPE toxicity has been attributed to reactive oxygen species (ROS) formation (Woodell and Rohrer 2014). Mice exposed to cigarette smoke exhibit signs of oxidative damage that recapitulate some symptoms of AMD, such as Bruch's membrane thickening, basal infoldings in the RPE, and RPE cell death (Fujihara et al. 2008). Smoking also promotes the formation of advanced glycation end-products (AGEs) (Kirkham et al. 2003) and deposition of cadmium, which promotes ROS production, in the RPE (Woodell and Rohrer 2014; Kirkham et al. 2003). Like smoking, obesity and high-fat diets have also been associated with early AMD and progression to late AMD (Cheung and Eaton 2013). The Beaver Dam Eye Study, for example, suggested a potential link between obesity and AMD (Howard et al. 2014). High glucose (Ghaem Maralani et al. 2015), high triglycerides (Ghaem Maralani et al. 2015), and daily red meat consumption (Ersoy et al. 2014) all appear to contribute to AMD risk. Collectively, these findings suggest lifestyle modifications may reduce the risk of AMD.

Because observations indicated diets rich in fruits and vegetables may protect against AMD (Ersoy et al. 2014; Seddon et al. 1994), the Age-Related Eye Disease Study (AREDS) (Age-Related Eye Disease Study Research 2001) was conducted to determine whether a dietary supplement containing high-dose vitamins C and E, beta carotene, and zinc could protect

against AMD progression by reducing oxidative stress (Cheung and Eaton 2013). A second study, AREDS2, tested lutein, zeaxanthin, and omega-3 fatty acids for AMD protection (Age-Related Eye Disease Study 2 Research G 2013). An initial report suggested the supplement slowed AMD progression (Age-Related Eye Disease Study Research 2001), but closer examination of the data suggested that it was ineffective (Ambati and Ambati 2002). Indeed, a meta-analysis of multiple AREDS trials indicated the supplement was ineffective (Evans 2008), a finding supported by follow-up examination of the original AREDS study participants (Chew et al. 2014). At the moment, lifestyle modification may be the only option to prevent the development and progression of AMD.

## 3 Previous Pharmacological Interventions

To date, there are no approved therapies effective at treating dry AMD despite decades of intensive research. Unlike neovascular AMD (Cheung and Eaton 2013; Schmidt-Erfurth et al. 2014), dry AMD continues to defy searches for a therapeutic target for intervention (Cheung and Eaton 2013). This section of the chapter will review both previous and current therapeutic interventions being tested for dry AMD treatment and the cell signaling pathways targeted by those interventions.

### 3.1 Antioxidants, Vitamins, and Herbal Supplements

Oxidative and mitochondrial stress may promote AMD development and progression (Hollyfield et al. 2008; Jarrett and Boulton 2012; Barot et al. 2011; Liang and Godley 2003), but to date, there are no effective therapies targeting oxidative damage or cellular oxidative response pathways. The AREDS dietary supplement formulations do not appear to be effective in preventing AMD progression (Age-Related Eye Disease Study Research G 2001; Evans 2008; Chew et al. 2014). Other herbal supplements and vitamin formulations not related to the AREDS and AREDS2 studies are also being studied for any potential efficacy against AMD progression. Some studies suggest *Ginkgo biloba* extract may protect against AMD by modulating choroidal blood flow and scavenging free radicals (Wilkinson and Fraunfelder 2011), and small trials conducted in Germany and France suggest the supplement may preserve vision in patients (Evans 2013). No large-scale clinical trials studying *G. biloba* extract have been conducted, however. Similarly, curcumin may inhibit the formation of oxidized lipids in oxidative stress conditions (Mandal et al. 2009), but no clinical trials have been performed yet. Resveratrol is also of interest because of its antioxidant activity (Pervaiz and Holme 2009), but given its limited testing in a clinical setting (Richer et al. 2014), results are inconclusive pending further investigation.

Other pharmacological interventions targeting the oxidative stress response include 5-hydroxytryptamine$_{1A}$ (5-HT$_{1A}$) agonists (Collier et al. 2011; Jaffe et al. 2015) and OT-551 (Wong et al. 2010). The 5-HT$_{1A}$ receptor is best known for its role in mediating serotonin-dependent signaling events involved in regulating sleep and anxiety, but receptor activation has also been demonstrated to protect against oxidative stress-induced RPE and photoreceptor cell death (Collier et al. 2011). The 5-HT$_{1A}$ agonists 8-hydroxy-2-(di-n-propylamino)-tetralin (8-OH-DPAT) and tandospirone (AL-8309A) protect against light-induced retinal damage in rodents (Collier et al. 2011; Biswal et al. 2015) by mitigating

oxidative damage to mitochondria (Biswal et al. 2015). Unfortunately, tandospirone was not found to prevent lesion growth in GA patients during a phase III trial (Jaffe et al. 2015), casting doubt on the potential utility of 5-$HT_{1A}$ agonists in treating dry AMD. Similarly, OT-551 (Evans and Syed 2013) appeared promising in preliminary studies but failed to significantly halt the GA lesion spread in a phase II clinical trial (Wong et al. 2010).

### 3.2 Visual Cycle Modulators

Analysis of eyecups obtained from AMD patients found increased amounts of N-retinyl-N-retinylidene ethanolamine (A2E) compared to eyecups obtained from healthy patients (Suter et al. 2000). Two molecules of all-*trans*-retinal (Redmond et al. 1998) react with ethanolamine in oxidative conditions to produce A2E (Suter et al. 2000), which accumulates in the RPE with age (Eldred 1995). A2E appeared to induce RPE toxicity by suppressing lysosomal function, suggesting visual cycle byproducts may contribute to AMD pathology (Suter et al. 2000). Because A2E is toxic to RPE and was thought to be a principal component of the autofluorescent material lipofuscin that appears in many AMD patients (Eldred 1995), several groups attempted to create therapeutics that could halt its formation and slow AMD progression.

Given the well-defined functional and biochemical role of the visual cycle protein RPE-specific protein 65 kDa (RPE65) (Redmond et al. 1998), inhibitors specific to RPE65 were developed to slow the rate of retinoid metabolism to slow A2E generation (Buschini et al. 2015; Zhang et al. 2015). Emixustat specifically binds RPE65 at its active site to inhibit its activity (Kubota et al. 2014). Later work found emixustat scavenges free retinoids as well, and that this activity heavily contributes to its mechanism-of-action (Zhang et al. 2015). Early phase I clinical trials tested the safety and tolerance of emixustat through oral administration of the drug in doses ranging from 5 to 40 mg over a 14-day period (Kubota et al. 2014). Two-thirds of patients experienced mild adverse reactions to the drug, and because these adverse reactions resolved at the end of the study (Kubota et al. 2014), emixustat proceeded to phase II/III clinical trial (Dugel et al. 2015). This clinical trial is expected to be completed by July 2016.

Fenretinide (N-4-hydroxyphenylretinamide) also targets retinoid metabolism to slow AMD progression. The synthetic retinoid was originally designed as a potential therapeutic to use against various cancers that require retinoids for tumorigenesis, but was found to be ineffective against cancer progression in phase II/III clinical trials (Malone et al. 2003). Similarly to emixustat, fenretinide reduces the total pool of vitamin A-derived retinoids needed to form A2E (Danis et al. 2015). Mechanistically, fenretinide binds to retinol-binding protein 4 (RBP4) in the serum to interfere with vitamin A transport to various tissues (Petrukhin 2013), effectively causing vitamin A to be cleared through the urine (Danis et al. 2015). Unfortunately, phase II clinical trial data indicated fenretinide did not significantly reduce the rate of lesion expansion in GA patients (Mata et al. 2013). There are no known plans to carry out a phase III clinical trial of fenretinide as a GA therapeutic agent (Danis et al. 2015). Other nonretinoid RBP4 antagonists (Cioffi et al. 2015) such as A1120 are also currently being tested for efficacy against AMD-like phenotypes in mouse models with high

rates of lipofuscinogenesis (Petrukhin 2013; Dobri et al. 2013), but these studies have not yet been translated to human patients.

### 3.3 Inflammatory Modulators

With the proliferation of studies suggesting pro-inflammatory pathways may be involved in AMD, anti-inflammatory agents are now of particular interest. A 1992 study reported elevated amounts of complement proteins C1q, C3c, and C3d in subretinal membranes removed from AMD patients (Baudouin et al. 1992). A series of landmark studies also identified the complement factor H Y402H ($CFH^{Y402H}$) polymorphism as the first heritable risk factor for AMD (Haines et al. 2005; Edwards et al. 2005; Klein et al. 2005), further highlighting the potential role of the complement cascade pathway in AMD pathogenesis. Unfortunately, the identification of both complement factor polymorphisms and complement factor proteins in AMD patients have not successfully facilitated the development of AMD therapeutics. The COMPLETE study (Yehoshua et al. 2014), which tested eculizumab, an anti-C5 antibody already approved for use in paroxysomal nocturnal hemoglobinuria (Buschini et al. 2015), found complement cascade inhibition had no effect on GA progression (Yehoshua et al. 2014). Similarly, the anti-C5 antibody LFG316 was ineffective in slowing or halting GA progression. Clinical trial data for another anti-C5 antibody, ARC1905, has not been published (Buschini et al. 2015). A neutralizing antibody targeting complement factor D (CFD) in GA patients, lampalizumab, is now in phase III trials (Danis et al. 2015).

Sirolimus, also known as rapamycin, has known anti-inflammatory properties (Mata and Vogel 2010). Already used as an immunosuppressant for organ transplant patients (Danis et al. 2015), it was hypothesized sirolimus may be effective in treating AMD as well because it was found to prevent RPE cell death in mouse models (Zhao et al. 2011). Two phase II clinical trials found no protective effect of sirolimus against GA, with no reported visual acuity protection or prevention of atrophic lesion spreading (Wong et al. 2013; Petrou et al. 2015).

Other efforts to treat AMD center on the NLRP3 inflammasome. A series of studies published within the last five years indicate DICER1 reduction in GA patients may contribute to RPE cell death because the enzyme is required to degrade cytotoxic *Alu* RNA transcripts (Kaneko et al. 2011). Increases in *Alu* RNA transcripts in GA patients cause activation of the NLRP3 inflammasome (Tarallo et al. 2012; Dridi et al. 2012), ultimately resulting in P2X7-dependent Caspase-8-mediated RPE cell death (Kerur et al. 2013; Kim et al. 2014). These observations are supported by other data showing this signaling pathway can be instigated by the presence of excess iron (Gelfand et al. 2015), which has also been previously associated with AMD in humans (Wong et al. 2007). It was recently found that nucleoside reverse transcriptase inhibitors (NRTIs), typically used to treat human immunodeficiency virus (HIV) patients, possessed anti-inflammatory properties because of their ability to block P2X7-dependent NLRP3 inflammasome activation (Wong et al. 2007). Preparations are currently underway to examine NRTIs in an AMD context in a clinical setting.

### 3.4 Neuroprotective Agents

Given the fact that blindness in GA is the direct result of photoreceptor death over regions with RPE atrophy (Danis et al. 2015), neuroprotective agents preventing photoreceptor cell apoptosis have been proposed as potential therapeutics. Ciliary neurotrophic factor (CNTF), for example, was previously demonstrated to preserve photoreceptor cell function and reduce apoptosis in various models of canine (Tao et al. 2002) and mouse retinal degeneration (LaVail et al. 1998). An encapsulated cell therapy (ECT)-based implant housing mammalian cells engineered to overproduce CNTF (Thanos et al. 2004) was injected into the eyes of GA patients in phase I (Sieving et al. 2006) and II clinical trials (Zhang et al. 2011). The CNTF-producing implant, NT-501 (Thanos et al. 2004), was found to be well-tolerated in patients (Sieving et al. 2006), but could not inhibit lesion spreading in GA patients (Zhang et al. 2011).

More recently, various groups have begun exploring the potential role of amyloid β in AMD. Amyloid β, perhaps best known for its suspected role in Alzheimer's disease (Kang et al. 1987; Hardy and Higgins 1992; Hardy and Selkoe 2002), was found to be a drusen component in AMD patients (Johnson et al. 2002; Dentchev et al. 2003). Ocular amyloid deposits in a mouse model of Alzheimer's disease were associated with retinal degeneration (Ning et al. 2008) and RPE stress (Ding et al. 2011), and amyloid β is known to activate the NLRP3 inflammasome (Halle et al. 2008), consistent with other findings that inflammasome activation may mediate GA (Tarallo et al. 2012; Kerur et al. 2013; Kim et al. 2014; Gelfand et al. 2015). Based on the studies suggesting amyloid β accumulation may contribute to ocular pathologies in mouse models of AMD (Ding et al. 2011; Catchpole et al. 2013), a clinical trial testing the efficacy of a monoclonal antibody against amyloid β is currently underway (Danis et al. 2015). The results of the phase II trial are not yet available.

### 3.5 Cell-Based Therapies

With the advent of human embryonic stem cell (hESC) and induced pluripotent stem cell (iPSC) technologies, recent therapeutic efforts focus on transplanting healthy derived RPE cells into GA patients (Danis et al. 2015). The first hESCs implanted into humans occurred in 2012 when hESCs were differentiated into RPE cells for subretinal implantation in patients with either Stargardt's disease or dry AMD (Schwartz et al. 2012). Following transplantation, patients were administered immunosuppressive drugs to prevent tissue rejection, and the patients were closely monitored for complications (Schwartz et al. 2012). Preliminary data indicate the therapy may be safe in human patients, but visual acuity improvements appeared marginal (Schwartz et al. 2012). A follow-up phase I/II clinical trial indicated a majority of patients who received RPE transplantation showed small regions of pigmentation several months following treatment, suggesting derived RPE cells injected into the eyes of patients could form a partial monolayer (Schwartz et al. 2015). Although the authors of the study claim visual acuity improvements in eyes receiving treatment compared to control eyes (Schwartz et al. 2015), the small patient sample is not currently sufficient to allow any definitive conclusions on whether hESC-derived RPE cells will effectively restore meaningful vision in AMD patients. The relatively small number of RPE cells surviving transplantation several months following treatments also suggests more refined methods of implantation using improved monolayers may be needed for these treatments to maximize

their efficacy (Brandl et al. 2015). iPSC-derived RPE cells may offer advantages over hESC-derived RPE cells with respect to long-term safety. Because iPSC-derived RPE cells allow for autologous transplantation, future patients will hopefully have less risk of transplant rejection and obviate the need for immunosuppressive drugs (Brandl et al. 2015). Clinical trials for iPSC-derived RPE cells are already underway, and a case study of a woman who received iPSC-derived RPE cell transplantation suggests they may be as safe as hESC-derived RPE cells (Forest et al. 2015). The results of these clinical trials will be forthcoming once they are complete.

## 4 Perspectives on Future Directions

Numerous lines of evidence suggest the field has long suffered from gaps in understanding with respect to basic AMD biology. The inability of the visual cycle therapeutic fenretinide to halt GA lesion growth (Danis et al. 2015; Mata et al. 2013), for example, supports this hypothesis. Fenretinide successfully depletes vitamin A in the serum (Danis et al. 2015) but has no effect on disease progression in humans. A primary reason fenretinide failed in clinical trials could be the fact that the field overestimated the importance of A2E in AMD pathogenesis. It was originally thought A2E correlated with AMD (Suter et al. 2000), but later work found A2E primarily accumulated in the periphery of AMD eyes (Bhosale et al. 2009), not in the macula. Furthermore, later work also demonstrated that lipofuscin only poorly predicted lesion spread in GA (Hwang et al. 2006) and that the presence of A2E and lipofuscin did not even correlate with one another (Ablonczy et al. 2013). Together, these data indicate A2E might be largely irrelevant to AMD and that visual cycle therapeutics like fenretinide would have little chance of having a protective effect in patients. Similarly, numerous clinical trials focused on targeting complement factors to prevent GA spread but were ultimately found ineffective. The biological relevance of CFH polymorphisms in and AMD context (Haines et al. 2005; Edwards et al. 2005; Klein et al. 2005) remains elusive; *Cfh* mutant mice show only a marginal phenotype (Coffey et al. 2007), and many individuals exhibiting complement deposition in the RPE never present with AMD (Anderson et al. 2010; Mullins et al. 2014). Thus, the field may be missing the biological understanding of AMD needed to create effective therapeutics.

Inadequate experimental design and data interpretation also confound efforts to treat dry AMD. The AREDS study, for example, originally reported the AREDS vitamin supplement could significantly slow the progression of AMD from its earlier to its more advanced stages, but further data analysis and later patient follow-up indicated AREDS was actually ineffective (Ambati and Ambati 2002; Evans 2008; Chew et al. 2014). Similarly, the role of the NLRP3 inflammasome with respect to AMD was at first unclear because of experimental design issues. After the NLRP3 inflammasome was linked to GA (Tarallo et al. 2012), the finding was challenged because of data demonstrating IL-18 antibody neutralization augmented laser-induced choroidal neovascularization in mice (Doyle et al. 2012). It was later found the IL-18 neutralizing antibody solution injected into mice contained glycerol, which is toxic to the retina and RPE; moreover, other laboratories could not replicate findings suggesting the NLRP3 inflammasome was protective (Ijima et al. 2014; Zhang et al. 2016; Wang et al. 2016; Tseng et al. 2013; Kauppinen et al. 2012; Hirano et al. 2014). In order for effective therapeutic options to become available to patients with dry AMD, the

field requires a better understanding of the basic biology underpinning disease pathogenesis, which in turn requires rigorous experimental design and analysis.

## 5 Conclusions

The complexity of AMD pathogenesis continues to stymie the development of effective pharmacological interventions for the disease. Unlike neovascular AMD, which has a number of therapeutic options for patients, dry AMD currently has no effective pharmacological intervention. Previous attempts to slow disease progression have been unsuccessful, but a new generation of novel pharmacological approaches and cell-based therapies may have a greater degree of success in treating the disease (Table 1).

## References

Ablonczy Z, Higbee D, Anderson DM, Dahrouj M, Grey AC, Gutierrez D, Koutalos Y, Schey KL, Hanneken A, Crouch RK. Lack of correlation between the spatial distribution of A2E and lipofuscin fluorescence in the human retinal pigment epithelium. Investig Ophthalmol Vis Sci. 2013; 54(8): 5535–5542. DOI: 10.1167/iovs.13-12250 [PubMed: 23847313]

Age-Related Eye Disease Study 2 Research G. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. JAMA. 2013; 309(19):2005–2015. DOI: 10.1001/jama.2013.4997 [PubMed: 23644932]

Age-Related Eye Disease Study Research G. 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 vision loss: AREDS report no. 8. Arch Ophthalmol. 2001; 119(10):1417–1436. [PubMed: 11594942]

Ambati J, Ambati BK. Age-related eye disease study caveats. Arch Ophthalmol. 2002; 120(7):997. author reply 997–999. [PubMed: 12096983]

Ambati J, Fowler BJ. Mechanisms of age-related macular degeneration. Neuron. 2012; 75(1):26–39. DOI: 10.1016/j.neuron.2012.06.018 [PubMed: 22794258]

Anderson DH, Radeke MJ, Gallo NB, Chapin EA, Johnson PT, Curletti CR, Hancox LS, Hu J, Ebright JN, Malek G, Hauser MA, Rickman CB, Bok D, Hageman GS, Johnson LV. The pivotal role of the complement system in aging and age-related macular degeneration: hypothesis re-visited. Prog Retin Eye Res. 2010; 29(2):95–112. DOI: 10.1016/j.preteyeres.2009.11.003 [PubMed: 19961953]

Barot M, Gokulgandhi MR, Mitra AK. Mitochondrial dysfunction in retinal diseases. Curr Eye Res. 2011; 36(12):1069–1077. DOI: 10.3109/02713683.2011.607536 [PubMed: 21978133]

Baudouin C, Peyman GA, Fredj-Reygrobellet D, Gordon WC, Lapalus P, Gastaud P, Bazan NG. Immunohistological study of subretinal membranes in age-related macular degeneration. Jpn J Ophthalmol. 1992; 36(4):443–451. [PubMed: 1289621]

Bhosale P, Serban B, Bernstein PS. Retinal carotenoids can attenuate formation of A2E in the retinal pigment epithelium. Arch Biochem Biophys. 2009; 483(2):175–181. DOI: 10.1016/j.abb. 2008.09.012 [PubMed: 18926795]

Biswal MR, Ahmed CM, Ildefonso CJ, Han P, Li H, Jivanji H, Mao H, Lewin AS. Systemic treatment with a 5HT1a agonist induces anti-oxidant protection and preserves the retina from mitochondrial oxidative stress. Exp Eye Res. 2015; 140:94–105. DOI: 10.1016/j.exer.2015.07.022 [PubMed: 26315784]

Bora NS, Matta B, Lyzogubov VV, Bora PS. Relationship between the complement system, risk factors and prediction models in age-related macular degeneration. Mol Immunol. 2014; doi: 10.1016/j.molimm.2014.07.012

Brandl C, Grassmann F, Riolfi J, Weber BH. Tapping stem cells to target AMD: challenges and prospects. J Clin Med. 2015; 4(2):282–303. DOI: 10.3390/jcm4020282 [PubMed: 26239128]

Buschini E, Fea AM, Lavia CA, Nassisi M, Pignata G, Zola M, Grignolo FM. Recent developments in the management of dry age-related macular degeneration. Clin Ophthalmol. 2015; 9:563–574. DOI: 10.2147/OPTH.S59724 [PubMed: 25878491]

Carr AJ, Smart MJ, Ramsden CM, Powner MB, da Cruz L, Coffey PJ. Development of human embryonic stem cell therapies for age-related macular degeneration. Trends Neurosci. 2013; 36(7): 385–395. DOI: 10.1016/j.tins.2013.03.006 [PubMed: 23601133]

Catchpole I, Germaschewski V, Hoh Kam J, Lundh von Leithner P, Ford S, Gough G, Adamson P, Overend P, Hilpert J, Lopez FJ, Ng YS, Coffey P, Jeffery G. Systemic administration of Abeta mAb reduces retinal deposition of Abeta and activated complement C3 in age-related macular degeneration mouse model. PLoS One. 2013; 8(6):e65518.doi: 10.1371/journal.pone.0065518 [PubMed: 23799019]

Cheung LK, Eaton A. Age-related macular degeneration. Pharmacotherapy. 2013; 33(8):838–855. DOI: 10.1002/phar.1264 [PubMed: 23580402]

Chew EY, Clemons TE, Agron E, Sperduto RD, Sangiovanni JP, Davis MD, Ferris FL 3rd, Age-Related Eye Disease Study Research G. Ten-year follow-up of age-related macular degeneration in the age-related eye disease study: AREDS report no. 36. JAMA Ophthalmol. 2014; 132(3):272–277. DOI: 10.1001/jamaophthalmol.2013.6636 [PubMed: 24385141]

Cioffi CL, Racz B, Freeman EE, Conlon MP, Chen P, Stafford DG, Schwarz DM, Zhu L, Kitchen DB, Barnes KD, Dobri N, Michelotti E, Cywin CL, Martin WH, Pearson PG, Johnson G, Petrukhin K. Bicyclic [3.3.0]-Octahydrocyclopenta[c]pyrrolo Antagonists of Retinol Binding Protein 4: Potential Treatment of Atrophic Age-Related Macular Degeneration and Stargardt Disease. J Med Chem. 2015; 58(15):5863–5888. DOI: 10.1021/acs.jmedchem.5b00423 [PubMed: 26181715]

Coffey PJ, Gias C, McDermott CJ, Lundh P, Pickering MC, Sethi C, Bird A, Fitzke FW, Maass A, Chen LL, Holder GE, Luthert PJ, Salt TE, Moss SE, Greenwood J. Complement factor H deficiency in aged mice causes retinal abnormalities and visual dysfunction. Proc Natl Acad Sci USA. 2007; 104(42):16651–16656. DOI: 10.1073/pnas.0705079104 [PubMed: 17921253]

Collier RJ, Patel Y, Martin EA, Dembinska O, Hellberg M, Krueger DS, Kapin MA, Romano C. Agonists at the serotonin receptor (5-HT(1A)) protect the retina from severe photo-oxidative stress. Investig Ophthalmol Vis Sci. 2011; 52(5):2118–2126. DOI: 10.1167/iovs.10-6304 [PubMed: 21087971]

Danis RP, Lavine JA, Domalpally A. Geographic atrophy in patients with advanced dry age-related macular degeneration: current challenges and future prospects. Clin Ophthalmol. 2015; 9:2159–2174. DOI: 10.2147/OPTH.S92359 [PubMed: 26640366]

Dentchev T, Milam AH, Lee VM, Trojanowski JQ, Dunaief JL. Amyloid-beta is found in drusen from some age-related macular degeneration retinas, but notin drusen from normal retinas. Mol Vis. 2003; 9:184–190. [PubMed: 12764254]

Ding J-D, Johnson LV, Herrmann R, Farsiu S, Smith SG, Groelle M, Mace BE, Sullivan P, Jamison JA, Kelly U, Harrabi O, Bollini SS, Dilley J, Kobayashi D, Kuang B, Li W, Pons J, Lin JC, Bowes Rickman C. Anti-amyloid therapy protects against retinal pigmented epithelium damage and vision loss in a model of age-related macular degeneration. Proc Natl Acad Sci U S A. 2011; 108(28):E279–E287. DOI: 10.1073/pnas.1100901108 [PubMed: 21690377]

Dobri N, Qin Q, Kong J, Yamamoto K, Liu Z, Moiseyev G, Ma JX, Allikmets R, Sparrow JR, Petrukhin K. A1120, a nonretinoid RBP4 antagonist, inhibits formation of cytotoxic bisretinoids in the animal model of enhanced retinal lipofuscinogenesis. Investig Ophthalmol Vis Sci. 2013; 54(1):85–95. DOI: 10.1167/iovs.12-10050 [PubMed: 23211825]

Doyle SL, Campbell M, Ozaki E, Salomon RG, Mori A, Kenna PF, Farrar GJ, Kiang AS, Humphries MM, Lavelle EC, O'Neill LA, Hollyfield JG, Humphries P. NLRP3 has a protective role in age-related macular degeneration through the induction of IL-18 by drusen components. Nat Med. 2012; 18(5):791–798. DOI: 10.1038/nm.2717 [PubMed: 22484808]

Dridi S, Hirano Y, Tarallo V, Kim Y, Fowler BJ, Ambati BK, Bogdanovich S, Chiodo VA, Hauswirth WW, Kugel JF, Goodrich JA, Ponicsan SL, Hinton DR, Kleinman ME, Baffi JZ, Gelfand BD, Ambati J. ERK1/2 activation is a therapeutic target in age-related macular degeneration. Proc Natl Acad Sci U S A. 2012; 109(34):13781–13786. DOI: 10.1073/pnas.1206494109 [PubMed: 22869729]

Dugel PU, Novack RL, Csaky KG, Richmond PP, Birch DG, Kubota R. Phase ii, randomized, placebo-controlled, 90-day study of emixustat hydrochloride in geographic atrophy associated with dry age-related macular degeneration. Retina. 2015; 35(6):1173–1183. DOI: 10.1097/IAE.0000000000000606 [PubMed: 25932553]

Edwards AO, Ritter R, Abel KJ, Manning A, Panhuysen C, Farrer LA. Complement factor H polymorphism and age-related macular degeneration. Science. 2005; 308(5720):421–424. DOI: 10.1126/science.1110189 [PubMed: 15761121]

Eldred GE. Lipofuscin fluorophore inhibits lysosomal protein degradation and may cause early stages of macular degeneration. Gerontology. 1995; 41(Suppl 2):15–28. [PubMed: 8821318]

Ersoy L, Ristau T, Lechanteur YT, Hahn M, Hoyng CB, Kirchhof B, den Hollander AI, Fauser S. Nutritional risk factors for age-related macular degeneration. BioMed Res Int. 2014; 2014:413150.doi: 10.1155/2014/413150 [PubMed: 25101280]

Evans J. Antioxidant supplements to prevent or slow down the progression of AMD: a systematic review and meta-analysis. Eye. 2008; 22(6):751–760. DOI: 10.1038/eye.2008.100 [PubMed: 18425071]

Evans JR. Ginkgo biloba extract for age-related macular degeneration. Cochrane Database Syst Rev. 2013; 1:CD001775.doi: 10.1002/14651858.CD001775.pub2

Evans JB, Syed BA. New hope for dry AMD? Nat Rev Drug Discov. 2013; 12(7):501–502. DOI: 10.1038/nrd4038 [PubMed: 23812264]

Ferris FL 3rd, Wilkinson CP, Bird A, Chakravarthy U, Chew E, Csaky K, Sadda SR, Beckman Initiative for Macular Research Classification C. Clinical classification of age-related macular degeneration. Ophthalmology. 2013; 120(4):844–851. DOI: 10.1016/j.ophtha.2012.10.036 [PubMed: 23332590]

Forest DL, Johnson LV, Clegg DO. Cellular models and therapies for age-related macular degeneration. Dis Model Mech. 2015; 8(5):421–427. DOI: 10.1242/dmm.017236 [PubMed: 26035859]

Fujihara M, Nagai N, Sussan TE, Biswal S, Handa JT. Chronic cigarette smoke causes oxidative damage and apoptosis to retinal pigmented epithelial cells in mice. PLoS One. 2008; 3(9):e3119.doi: 10.1371/journal.pone.0003119 [PubMed: 18769672]

Gelfand BD, Wright CB, Kim Y, Yasuma T, Yasuma R, Li S, Fowler BJ, Bastos-Carvalho A, Kerur N, Uittenbogaard A, Han YS, Lou D, Kleinman ME, McDonald WH, Nunez G, Georgel P, Dunaief JL, Ambati J. Iron toxicity in the retina requires Alu RNA and the NLRP3 inflammasome. Cell Rep. 2015; 11(11):1686–1693. DOI: 10.1016/j.celrep.2015.05.023 [PubMed: 26074074]

Ghaem Maralani H, Tai BC, Wong TY, Tai ES, Li J, Wang JJ, Mitchell P. Metabolic syndrome and risk of age-related macular degeneration. Retina. 2015; 35(3):459–466. DOI: 10.1097/IAE.0000000000000338 [PubMed: 25207946]

Haines JL, Hauser MA, Schmidt S, Scott WK, Olson LM, Gallins P, Spencer KL, Kwan SY, Noureddine M, Gilbert JR, Schnetz-Boutaud N, Agarwal A, Postel EA, Pericak-Vance MA. Complement factor H variant increases the risk of age-related macular degeneration. Science. 2005; 308(5720):419–421. DOI: 10.1126/science.1110359 [PubMed: 15761120]

Halle A, Hornung V, Petzold GC, Stewart CR, Monks BG, Reinheckel T, Fitzgerald KA, Latz E, Moore KJ, Golenbock DT. The NALP3 inflammasome is involved in the innate immune response to amyloid-beta. Nat Immunol. 2008; 9(8):857–865. DOI: 10.1038/ni.1636 [PubMed: 18604209]

Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. Science. 1992; 256(5054):184–185. [PubMed: 1566067]

Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. 2002; 297(5580):353–356. DOI: 10.1126/science.1072994 [PubMed: 12130773]

Hirano Y, Yasuma T, Mizutani T, Fowler BJ, Tarallo V, Yasuma R, Kim Y, Bastos-Carvalho A, Kerur N, Gelfand BD, Bogdanovich S, He S, Zhang X, Nozaki M, Ijima R, Kaneko H, Ogura Y, Terasaki H, Nagai H, Haro I, Nunez G, Ambati BK, Hinton DR, Ambati J. IL-18 is not therapeutic for neovascular age-related macular degeneration. Nat Med. 2014; 20(12):1372–1375. DOI: 10.1038/nm.3671 [PubMed: 25473914]

Hollyfield JG, Bonilha VL, Rayborn ME, Yang X, Shadrach KG, Lu L, Ufret RL, Salomon RG, Perez VL. Oxidative damage-induced inflammation initiates age-related macular degeneration. Nat Med. 2008; 14(2):194–198. DOI: 10.1038/nm1709 [PubMed: 18223656]

Howard KP, Klein BE, Lee KE, Klein R. Measures of body shape and adiposity as related to incidence of age-related eye diseases: observations from the Beaver Dam Eye Study. Investig Ophthalmol Vis Sci. 2014; 55(4):2592–2598. DOI: 10.1167/iovs.13-13763 [PubMed: 24667857]

Hwang JC, Chan JW, Chang S, Smith RT. Predictive value of fundus autofluorescence for development of geographic atrophy in age-related macular degeneration. Investig Ophthalmol Vis Sci. 2006; 47(6):2655–2661. DOI: 10.1167/iovs.05-1027 [PubMed: 16723483]

Ijima R, Kaneko H, Ye F, Nagasaka Y, Takayama K, Kataoka K, Kachi S, Iwase T, Terasaki H. Interleukin-18 induces retinal pigment epithelium degeneration in mice. Investig Ophthalmol Vis Sci. 2014; 55(10):6673–6678. DOI: 10.1167/iovs.14-15367 [PubMed: 25237159]

Jaffe GJ, Schmitz-Valckenberg S, Boyer D, Heier J, Wolf-Schnurrbusch U, Staurenghi G, Schmidt-Erfurth U, Holz FG. Randomized trial to evaluate tandospirone in geographic atrophy secondary to age-related macular degeneration: The GATE Study. Am J Ophthalmol. 2015; 160(6):1226–1234. DOI: 10.1016/j.ajo.2015.08.024 [PubMed: 26310670]

Jarrett SG, Boulton ME. Consequences of oxidative stress in age-related macular degeneration. Mol Aspects Med. 2012; 33(4):399–417. DOI: 10.1016/j.mam.2012.03.009 [PubMed: 22510306]

Johnson LV, Leitner WP, Rivest AJ, Staples MK, Radeke MJ, Anderson DH. The Alzheimer's A beta -peptide is deposited at sites of complement activation in pathologic deposits associated with aging and age-related macular degeneration. Proc Natl Acad Sci U S A. 2002; 99(18):11830–11835. DOI: 10.1073/pnas.192203399 [PubMed: 12189211]

Kaneko H, Dridi S, Tarallo V, Gelfand BD, Fowler BJ, Cho WG, Kleinman ME, Ponicsan SL, Hauswirth WW, Chiodo VA, Karikó K, Yoo JW, Lee D-K, Hadziahmetovic M, Song Y, Misra S, Chaudhuri G, Buaas FW, Braun RE, Hinton DR, Zhang Q, Grossniklaus HE, Provis JM, Madigan MC, Milam AH, Justice NL, Albuquerque RJC, Blandford AD, Bogdanovich S, Hirano Y, Witta J, Fuchs E, Littman DR, Ambati BK, Rudin CM, Chong MMW, Provost P, Kugel JF, Goodrich JA, Dunaief JL, Baffi JZ, Ambati J. DICER1 deficit induces Alu RNA toxicity in age-related macular degeneration. Nature. 2011; doi: 10.1038/nature09830

Kang J, Lemaire HG, Unterbeck A, Salbaum JM, Masters CL, Grzeschik KH, Multhaup G, Beyreuther K, Muller-Hill B. The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor. Nature. 1987; 325(6106):733–736. DOI: 10.1038/325733a0 [PubMed: 2881207]

Kauppinen A, Niskanen H, Suuronen T, Kinnunen K, Salminen A, Kaarniranta K. Oxidative stress activates NLRP3 inflammasomes in ARPE-19 cells–implications for age-related macular degeneration (AMD). Immunol Lett. 2012; 147(1–2):29–33. DOI: 10.1016/j.imlet.2012.05.005 [PubMed: 22698681]

Kerur N, Hirano Y, Tarallo V, Fowler BJ, Bastos-Carvalho A, Yasuma T, Yasuma R, Kim Y, Hinton DR, Kirschning CJ, Gelfand BD, Ambati J. TLR-independent and P2X7-dependent signaling mediate Alu RNA-induced NLRP3 inflammasome activation in geographic atrophy. Investig Ophthalmol Vis Sci. 2013; 54(12):7395–7401. DOI: 10.1167/iovs.13-12500 [PubMed: 24114535]

Kim Y, Tarallo V, Kerur N, Yasuma T, Gelfand BD, Bastos-Carvalho A, Hirano Y, Yasuma R, Mizutani T, Fowler BJ, Li S, Kaneko H, Bogdanovich S, Ambati BK, Hinton DR, Hauswirth WW, Hakem R, Wright C, Ambati J. DICER1/Alu RNA dysmetabolism induces Caspase-8-mediated cell death in age-related macular degeneration. Proc Natl Acad Sci U S A. 2014; 111(45):16082–16087. DOI: 10.1073/pnas.1403814111 [PubMed: 25349431]

Kirkham PA, Spooner G, Ffoulkes-Jones C, Calvez R. Cigarette smoke triggers macrophage adhesion and activation: role of lipid peroxidation products and scavenger receptor. Free Radic Biol Med. 2003; 35(7):697–710. [PubMed: 14583334]

Klein R, Klein BE, Franke T. The relationship of cardiovascular disease and its risk factors to age-related maculopathy. The Beaver Dam Eye Study. Ophthalmology. 1993; 100(3):406–414. [PubMed: 8460013]

Klein RJ, Zeiss C, Chew EY, Tsai J-Y, Sackler RS, Haynes C, Henning AK, SanGiovanni JP, Mane SM, Mayne ST, Bracken MB, Ferris FL, Ott J, Barnstable C, Hoh J. Complement factor H polymorphism in age-related macular degeneration. Science. 2005; 308(5720):385–389. DOI: 10.1126/science.1109557 [PubMed: 15761122]

Kubota R, Al-Fayoumi S, Mallikaarjun S, Patil S, Bavik C, Chandler JW. Phase 1, doseranging study of emixustat hydrochloride (ACU-4429), a novel visual cycle modulator, in healthy volunteers. Retina. 2014; 34(3):603–609. DOI: 10.1097/01.iae.0000434565.80060.f8 [PubMed: 24056528]

LaVail MM, Yasumura D, Matthes MT, Lau-Villacorta C, Unoki K, Sung CH, Steinberg RH. Protection of mouse photoreceptors by survival factors in retinal degenerations. Investig Ophthalmol Vis Sci. 1998; 39(3):592–602. [PubMed: 9501871]

Liang FQ, Godley BF. Oxidative stress-induced mitochondrial DNA damage inhuman retinal pigment epithelial cells: a possible mechanism for RPE aging and age-related macular degeneration. Exp Eye Res. 2003; 76(4):397–403. [PubMed: 12634104]

Malone W, Perloff M, Crowell J, Sigman C, Higley H. Fenretinide: a prototype cancer prevention drug. Expert Opin Investig Drugs. 2003; 12(11):1829–1842. DOI: 10.1517/13543784.12.11.1829

Mandal MN, Patlolla JM, Zheng L, Agbaga MP, Tran JT, Wicker L, Kasus-Jacobi A, Elliott MH, Rao CV, Anderson RE. Curcumin protects retinal cells from light-and oxidant stress-induced cell death. Free Radic Biol Med. 2009; 46(5):672–679. DOI: 10.1016/j.freeradbiomed.2008.12.006 [PubMed: 19121385]

Mata NL, Vogel R. Pharmacologic treatment of atrophic age-related macular degeneration. Curr Opin Ophthalmol. 2010; 21(3):190–196. DOI: 10.1097/ICU.0b013e32833866c8 [PubMed: 20216419]

Mata NL, Lichter JB, Vogel R, Han Y, Bui TV, Singerman LJ. Investigation of oral fenretinide for treatment of geographic atrophy in age-related macular degeneration. Retina. 2013; 33(3):498–507. DOI: 10.1097/IAE.0b013e318265801d [PubMed: 23023528]

Mitchell P, Smith W, Attebo K, Wang JJ. Prevalence of age-related maculopathy in Australia. The Blue Mountains Eye Study. Ophthalmology. 1995; 102(10):1450–1460. [PubMed: 9097791]

Mullins RF, Schoo DP, Sohn EH, Flamme-Wiese MJ, Workamelahu G, Johnston RM, Wang K, Tucker BA, Stone EM. The membrane attack complex in aging human choriocapillaris: relationship to macular degeneration and choroidal thinning. Am J Pathol. 2014; 184(11):3142–3153. DOI: 10.1016/j.ajpath.2014.07.017 [PubMed: 25204844]

Ning A, Cui J, To E, Ashe KH, Matsubara J. Amyloid-beta deposits lead to retinal degeneration in a mouse model of Alzheimer disease. Investig Ophthalmol Vis Sci. 2008; 49(11):5136–5143. DOI: 10.1167/iovs.08-1849 [PubMed: 18566467]

Pervaiz S, Holme AL. Resveratrol: its biologic targets and functional activity. Antioxid Redox Signal. 2009; 11(11):2851–2897. DOI: 10.1089/ARS.2008.2412 [PubMed: 19432534]

Petrou PA, Cunningham D, Shimel K, Harrington M, Hammel K, Cukras CA, Ferris FL, Chew EY, Wong WT. Intravitreal sirolimus for the treatment of geographic atrophy: results of a phase I/II clinical trial. Investig Ophthalmol Vis Sci. 2015; 56(1):330–338. DOI: 10.1167/iovs.14-15877

Petrukhin K. Pharmacological inhibition of lipofuscin accumulation in the retina as a therapeutic strategy for dry AMD treatment. Drug Discov Today Ther Strateg. 2013; 10(1):e11–e20. DOI: 10.1016/j.ddstr.2013.05.004 [PubMed: 25152755]

Ratnapriya R, Chew EY. Age-related macular degeneration-clinical review and genetics update. Clin Genet. 2013; 84(2):160–166. DOI: 10.1111/cge.12206 [PubMed: 23713713]

Redmond TM, Yu S, Lee E, Bok D, Hamasaki D, Chen N, Goletz P, Ma JX, Crouch RK, Pfeifer K. Rpe65 is necessary for production of11-cis-vitamin Ain the retinal visual cycle. Nat Genet. 1998; 20(4):344–351. [PubMed: 9843205]

Rein DB, Wittenborn JS, Zhang X, Honeycutt AA, Lesesne SB, Saaddine J, Vision Health Cost-Effectiveness Study G. Forecasting age-related macular degeneration through the year 2050: the potential impact of new treatments. Arch Ophthalmol. 2009; 127(4):533–540. DOI: 10.1001/archophthalmol.2009.58 [PubMed: 19365036]

Richer S, Patel S, Sockanathan S, Ulanski LJ 2nd, Miller L, Podella C. Resveratrol based oral nutritional supplement produces long-term beneficial effects on structure and visual function in human patients. Nutrients. 2014; 6(10):4404–4420. DOI: 10.3390/nu6104404 [PubMed: 25329968]

Schmidt-Erfurth U, Chong V, Loewenstein A, Larsen M, Souied E, Schlingemann R, Eldem B, Mones J, Richard G, Bandello F, European Society of Retina Specialists. Guidelines for the management of neovascular age-related macular degeneration by the European Society of Retina Specialists

(EURETINA). Br J Ophthalmol. 2014; 98(9):1144–1167. DOI: 10.1136/bjophthalmol-2014-305702 [PubMed: 25136079]

Schmier JK, Covert DW, Lau EC. Patterns and costs associated with progression of age-related macular degeneration. Am J Ophthalmol. 2012; 154(4):675–681. e671. DOI: 10.1016/j.ajo.2012.04.017 [PubMed: 22835513]

Schwartz SD, Hubschman JP, Heilwell G, Franco-Cardenas V, Pan CK, Ostrick RM, Mickunas E, Gay R, Klimanskaya I, Lanza R. Embryonic stem cell trials for macular degeneration: a preliminary report. Lancet. 2012; 379(9817):713–720. DOI: 10.1016/S0140-6736(12)60028-2 [PubMed: 22281388]

Schwartz SD, Regillo CD, Lam BL, Eliott D, Rosenfeld PJ, Gregori NZ, Hubschman JP, Davis JL, Heilwell G, Spirn M, Maguire J, Gay R, Bateman J, Ostrick RM, Morris D, Vincent M, Anglade E, Del Priore LV, Lanza R. Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies. Lancet. 2015; 385(9967):509–516. DOI: 10.1016/S0140-6736(14)61376-3 [PubMed: 25458728]

Seddon JM, Ajani UA, Sperduto RD, Hiller R, Blair N, Burton TC, Farber MD, Gragoudas ES, Haller J, Miller DT, et al. Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. Eye Disease Case-Control Study Group. JAMA. 1994; 272(18):1413–1420. [PubMed: 7933422]

Sieving PA, Caruso RC, Tao W, Coleman HR, Thompson DJ, Fullmer KR, Bush RA. Ciliary neurotrophic factor (CNTF) for human retinal degeneration: phase I trial of CNTF delivered by encapsulated cell intraocular implants. Proc Natl Acad Sci U S A. 2006; 103(10):3896–3901. DOI: 10.1073/pnas.0600236103 [PubMed: 16505355]

Smith W, Assink J, Klein R, Mitchell P, Klaver CC, Klein BE, Hofman A, Jensen S, Wang JJ, de Jong PT. Risk factors for age-related macular degeneration: pooled findings from three continents. Ophthalmology. 2001; 108(4):697–704. [PubMed: 11297486]

Suter M, Reme C, Grimm C, Wenzel A, Jaattela M, Esser P, Kociok N, Leist M, Richter C. Age-related macular degeneration. The lipofusion component N-retinyl-N-retinylidene ethanolamine detaches proapoptotic proteins from mitochondria and induces apoptosis in mammalian retinal pigment epithelial cells. J Biol Chem. 2000; 275(50):39625–39630. DOI: 10.1074/jbc.M007049200 [PubMed: 11006290]

Tao W, Wen R, Goddard MB, Sherman SD, O'Rourke PJ, Stabila PF, Bell WJ, Dean BJ, Kauper KA, Budz VA, Tsiaras WG, Acland GM, Pearce-Kelling S, Laties AM, Aguirre GD. Encapsulated cell-based deliveryof CNTF reduces photoreceptor degeneration in animal models of retinitis pigmentosa. Investig Ophthalmol Vis Sci. 2002; 43(10):3292–3298. [PubMed: 12356837]

Tarallo V, Hirano Y, Gelfand BD, Dridi S, Kerur N, Kim Y, Cho WG, Kaneko H, Fowler BJ, Bogdanovich S, Albuquerque RJ, Hauswirth WW, Chiodo VA, Kugel JF, Goodrich JA, Ponicsan SL, Chaudhuri G, Murphy MP, Dunaief JL, Ambati BK, Ogura Y, Yoo JW, Lee DK, Provost P, Hinton DR, Nunez G, Baffi JZ, Kleinman ME, Ambati J. DICER1 loss and Alu RNA induce age-related macular degeneration via the NLRP3 inflammasome and MyD88. Cell. 2012; 149(4):847–859. DOI: 10.1016/j.cell.2012.03.036 [PubMed: 22541070]

Thanos CG, Bell WJ, O'Rourke P, Kauper K, Sherman S, Stabila P, Tao W. Sustained secretion of ciliary neurotrophic factor to the vitreous, using the encapsulated cell therapy-based NT-501 intraocular device. Tissue Eng. 2004; 10(11–12):1617–1622. DOI: 10.1089/ten.2004.10.1617 [PubMed: 15684670]

Tseng WA, Thein T, Kinnunen K, Lashkari K, Gregory MS, D'Amore PA, Ksander BR. NLRP3 inflammasome activation in retinal pigment epithelial cellsbylysosomal destabilization: implications for age-related macular degeneration. Investig Ophthalmol Vis Sci. 2013; 54(1):110–120. DOI: 10.1167/iovs.12-10655 [PubMed: 23221073]

Velilla S, Garcia-Medina JJ, Garcia-Layana A, Dolz-Marco R, Pons-Vazquez S, Pinazo-Duran MD, Gomez-Ulla F, Arevalo JF, Diaz-Llopis M, Gallego-Pinazo R. Smoking and age-related macular degeneration: review and update. J Ophthalmol. 2013; 2013:895147.doi: 10.1155/2013/895147 [PubMed: 24368940]

Vingerling JR, Dielemans I, Hofman A, Grobbee DE, Hijmering M, Kramer CF, de Jong PT. The prevalence of age-related maculopathy in the Rotterdam Study. Ophthalmology. 1995; 102(2):205–210. [PubMed: 7862408]

Wang Y, Hanus JW, Abu-Asab MS, Shen D, Ogilvy A, Ou J, Chu XK, Shi G, Li W, Wang S, Chan CC. NLRP3 upregulation in retinal pigment epithelium in age-related macular degeneration. Int J Mol Sci. 2016; 17(1):73.doi: 10.3390/ijms17010073

Wilkinson JT, Fraunfelder FW. Use of herbal medicines and nutritional supplements in ocular disorders: an evidence-based review. Drugs. 2011; 71(18):2421–2434. DOI: 10.2165/11596840-000000000-00000 [PubMed: 22141385]

Wong RW, Richa DC, Hahn P, Green WR, Dunaief JL. Iron toxicity as a potential factor in AMD. Retina. 2007; 27(8):997–1003. DOI: 10.1097/IAE.0b013e318074c290 [PubMed: 18040235]

Wong TY, Chakravarthy U, Klein R, Mitchell P, Zlateva G, Buggage R, Fahrbach K, Probst C, Sledge I. The natural history and prognosis of neovascular age-related macular degeneration: a systematic review of the literature and meta-analysis. Ophthalmology. 2008; 115(1):116–126. DOI: 10.1016/j.ophtha.2007.03.008 [PubMed: 17675159]

Wong WT, Kam W, Cunningham D, Harrington M, Hammel K, Meyerle CB, Cukras C, Chew EY, Sadda SR, Ferris FL. Treatment of geographic atrophy by the topical administration of OT-551: results of a phase II clinical trial. Investig Ophthalmol Vis Sci. 2010; 51(12):6131–6139. DOI: 10.1167/iovs.10-5637 [PubMed: 20574018]

Wong WT, Dresner S, Forooghian F, Glaser T, Doss L, Zhou M, Cunningham D, Shimel K, Harrington M, Hammel K, Cukras CA, Ferris FL, Chew EY. Treatment of geographic atrophy with subconjunctival sirolimus: results of a phase I/II clinical trial. Investig Ophthalmol Vis Sci. 2013; 54(4):2941–2950. DOI: 10.1167/iovs.13-11650 [PubMed: 23548622]

Woodell A, Rohrer B. A mechanistic review of cigarette smoke and age-related macular degeneration. Adv Exp Med Biol. 2014; 801:301–307. DOI: 10.1007/978-1-4614-3209-8_38 [PubMed: 24664711]

Yehoshua Z, de Amorim Garcia Filho CA, Nunes RP, Gregori G, Penha FM, Moshfeghi AA, Zhang K, Sadda S, Feuer W, Rosenfeld PJ. Systemic complement inhibition with eculizumab for geographic atrophy in age-related macular degeneration: the COMPLETE study. Ophthalmology. 2014; 121(3):693–701. DOI: 10.1016/j.ophtha.2013.09.044 [PubMed: 24289920]

Zeng S, Whitmore SS, Sohn EH, Riker MJ, Wiley LA, Scheetz TE, Stone EM, Tucker BA, Mullins RF. Molecular response of chorioretinal endothelial cells to complement injury: implications for macular degeneration. J Pathol. 2016; 238(3):446–456. DOI: 10.1002/path.4669 [PubMed: 26564985]

Zhang K, Hopkins JJ, Heier JS, Birch DG, Halperin LS, Albini TA, Brown DM, Jaffe GJ, Tao W, Williams GA. Ciliary neurotrophic factor delivered by encapsulated cell intraocular implants for treatment of geographic atrophy in age-related macular degeneration. Proc Natl Acad Sci U S A. 2011; 108(15):6241–6245. DOI: 10.1073/pnas.1018987108 [PubMed: 21444807]

Zhang J, Kiser PD, Badiee M, Palczewska G, Dong Z, Golczak M, Tochtrop GP, Palczewski K. Molecular pharmacodynamics of emixustat in protection against retinal degeneration. J Clin Invest. 2015; 125(7):2781–2794. DOI: 10.1172/JCI80950 [PubMed: 26075817]

Zhang S, Yu N, Zhang R, Zhang S, Wu J. Interleukin-17A induces IL-1beta secretion from RPE cells via the NLRP3 inflammasome. Investig Ophthalmol Vis Sci. 2016; 57(2):312–319. DOI: 10.1167/iovs.15-17578 [PubMed: 26830368]

Zhao C, Yasumura D, Li X, Matthes M, Lloyd M, Nielsen G, Ahern K, Snyder M, Bok D, Dunaief JL, LaVail MM, Vollrath D. mTOR-mediated dedifferentiation of the retinal pigment epithelium initiates photoreceptor degeneration in mice. J Clin Invest. 2011; 121(1):369–383. DOI: 10.1172/JCI44303 [PubMed: 21135502]

**Table 1**

Therapeutics tested in the clinic for dry AMD

| Agent | Intervention | Targeted biology |
|---|---|---|
| AREDS supplement | Dietary supplement | Oxidative stress |
| *G. biloba* extract | Dietary supplement | Oxidative stress |
| Curcumin | Dietary supplement | Oxidative stress |
| Resveratrol | Dietary supplement | Oxidative stress |
| 8-OH-DPAT | Small molecule | Oxidative stress |
| Tandospirone (AL-8309A) | Small molecule | Oxidative stress |
| OT-551 | Small molecule | Oxidative stress |
| Emixustat[a] | Small molecule | Visual cycle |
| Fenretinide | Small molecule | Visual cycle |
| A1120 | Small molecule | Visual cycle |
| Eculizumab | Antibody | Complement cascade |
| LFG316 | Antibody | Complement cascade |
| ARC1905 | Antibody | Complement cascade |
| Lampalizumab[a] | Antibody | Complement cascade |
| Rapamycin | Small molecule | Inflammation (mTOR signaling) |
| CNTF | Recombinant protein | Neuroprotection |
| GSK 933776[a] | Antibody | Amyloid-β aggregation |
| iPSC-derived RPE[a] | Cell-based therapy | RPE loss |

[a]Clinical trials have not yet been completed