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Cell-based therapeutic strategies for replacement and preservation in retinal degenerative diseases

Melissa K. Jones[a,b], **Bin Lu**[a,b], **Sergey Girman**[a,b], and **Shaomei Wang**[a,b,c,*]

[a]Board of Governors Regenerative Medicine Institute, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, CA 90048, USA

[b]Department of Biomedical Sciences, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, CA 90048, USA

[c]David Geffen School of Medicine, University of California Los Angeles, 10833 Le Conte Ave., Los Angeles, CA 90095, USA

Abstract

Cell-based therapeutics offer diverse options for treating retinal degenerative diseases, such as age-related macular degeneration (AMD) and retinitis pigmentosa (RP). AMD is characterized by both genetic and environmental risks factors, whereas RP is mainly a monogenic disorder. Though treatments exist for some patients with neovascular AMD, a majority of retinal degenerative patients have no effective therapeutics, thus indicating a need for universal therapies to target diverse patient populations. Two main cell-based mechanistic approaches are being tested in clinical trials. Replacement therapies utilize cell-derived retinal pigment epithelial (RPE) cells to supplant lost or defective host RPE cells. These cells are similar in morphology and function to native RPE cells and can potentially supplant the responsibilities of RPE *in vivo*. Preservation therapies utilize supportive cells to aid in visual function and photoreceptor preservation partially by neurotrophic mechanisms. The goal of preservation strategies is to halt or slow the progression of disease and maintain remaining visual function. A number of clinical trials are testing the safety of replacement and preservation cell therapies in patients; however, measures of efficacy will need to be further evaluated. In addition, a number of prevailing concerns with regards to the immune-related response, longevity, and functionality of the grafted cells will need to be addressed in future trials. This review will summarize the current status of cell-based preclinical and clinical studies with a focus on replacement and preservation strategies and the obstacles that remain regarding these types of treatments.

*Corresponding author: Shaomei Wang, Cedars-Sinai Medical Center, Board of Governors Regenerative Medicine Institute, 8700 Beverly Boulevard, Los Angeles, California, 90048; Telephone: (310)248-8576; Fax: (310)248-8555; shaomei.wang@cshs.org.

Keywords

Age-related macular degeneration; animal models; retinitis pigmentosa; stem cell therapy; transplantation; visual function

1. Introduction

1.1. Global impact and significance

The eye is a complex, remarkable organ that allows for the translation of visual light into biological signals that are interpreted by the brain for perception of the world. Even with over a century of study, researchers are still identifying all of the intricacies of how the eye develops and functions, the mechanisms of disease progression and loss of sight, and new innovations to prevent blindness (Donders, 1864; Hutchison and Tay, 1875). Mysteries such as these have enabled a rich culture in ground-breaking vision research with advancements in technologies aimed at treating a diverse group of diseases.

Outside the biological aspects, vision deficits are also a social burden. A large patient population exists with the global prevalence of blindness at over 30 million and over 190 million with visual impairments (Stevens et al., 2013). Visual deterioration also affects patients' mental health and quality of life, as many neurodegenerative diseases are progressive and have no cures (Yuzawa et al., 2013). In addition, there is a considerable economic burden for patients, the healthcare system, and society in whole. The estimated global cost is at $3.0 trillion USD, and expected to increase with the growth of the aging population and geriatric care (Gordois et al., 2012; Koberlein et al., 2013). Finding an effective and safe treatment for retinal degenerative diseases would not only help patients but also reduce the economic burden on society.

1.2. Advantages of treating retinal degenerative diseases

In comparison to other organs of the human body, the eye has numerous advantages as an ideal candidate for therapeutic intervention. Since the eyes are one of the few paired organs, one eye can be treated while the contralateral eye serves as an internal control. Visual function is independent of organ duality, such that if one is lost or damaged then the fellow eye can perform relatively autonomously. Additionally, having both internal and external components make it easily accessible for surgical intervention, and multiple routes of access allow for specificity of tissue targets. Ophthalmic examinations such as optical coherence tomography (OCT), electroretinography (ERG), and visual acuity testing are able to detect visual function and inner and outer nuclear layer thickness (Berson et al., 1996; Lim et al., 2008). Advances in *in vivo* imaging systems, such as adaptive optics scanning laser ophthalmoscopy (AOSLO) and spectral domain OCT (SD-OCT), allows for the monitoring of retinal lamination, oxygenation in blood vessels, cellular changes, progression of disease, and response to treatments (Bizheva et al., 2006; Freeman et al., 2010; Holmgren, 1865; Huang et al., 1991; Huber et al., 2009; Kagemann et al., 2007; Muraoka et al., 2012; Novais et al., 2016; Pron, 2014; Srinivasan et al., 2007; Toth et al., 1997; Zayit-Soudry et al., 2013).

The lens acts as a window to the interior and posterior components, including the retina, macula, optic nerve, and blood vessels, for examination and diagnosis. Functional assessments, such as visual acuity tests and electroretinography (ERG), can be routinely and inexpensively performed for monitoring vision (Kahn and Lowenstein, 1924; Snellen, 1862). In addition to the structural and anatomical benefits, the intact eye is largely considered an immune-privileged site because it can support grafted tissue or cells for extended or indefinite periods of time without rejection (Medawar, 1948; Streilein et al., 2002). The benefit of immune-privilege is that tissues with limited regenerative capacity are protected from uncontrolled immune responses, but in cases of injury, damage, or degeneration in the eye, then this protection is compromised and causes immune cell infiltration necessary for repair (Benhar et al., 2012; Frank and Wolburg, 1996; London et al., 2011). With numerous advancements in technology and the convenience of accessing ocular tissues, vision and ophthalmic research continues to be advantageous for both patients and scientists.

1.3. Interconnection between photoreceptor and retinal pigment epithelial cells

The retina is a laminar structure that consists of numerous highly interconnected different cell types and neural processes, and each plays a particular role in the processing of visual signals. The neural retina is located at the posterior portion of the eye and is adjacent to the retinal pigment epithelium (RPE). Visual signaling starts at the light-sensitive photoreceptor cells located in the outer neural retina, and their cell bodies reside within the outer nuclear layer (ONL). In the human retina, two types of photoreceptor cells, rods and cones, are responsible for different functions of vision. Rods are predominately located in the peripheral retina and are responsible for low light vision. Conversely, cones are densely located in the central portion of the retina, termed the macula, and are accountable for high-resolution central color vision. Visual signals travel from the photoreceptors to the bipolar cells located in the inner nuclear layer (INL) which relay to retinal ganglion cells (RGCs) to eventually reach the brain via the optic nerve. Communication between the ONL, INL, and RGCs is aided by horizontal and amacrine cells, which reside in the INL and RGC layer. Due to the complexity within the retina, cellular and synaptic disruptions can cause visual deficits, and specifically, degeneration or loss of function of photoreceptor cells leads to permanent vision loss.

Photoreceptor and RPE cells are interdependent for proper differentiation and function. During development, neuroepithelial cells comprise two layers that will become the RPE cells and neuronal retina (Strauss, 2005). These layers are separated by a thin lumen which forms the interphotoreceptor matrix (IPM) and allows for maturation of the RPE (Gonzalez-Fernandez and Healy, 1990; Gonzalez-Fernandez et al., 1993). The RPE forms as a monolayer of pigmented cells that acts as the outer blood retina-barrier to regulate trafficking of solutes from the choroid to the subretinal space and photoreceptor cells (Campbell and Humphries, 2012). The inner blood-retina barrier is composed of the retinal vascular endothelial cells and mediates movement of molecules from the blood to the inner retina (Campbell and Humphries, 2012; Rizzolo, 1997; Steinberg, 1985). The RPE basement membrane forms the inner layer of the Bruch’s membrane that separates the RPE from the choriocapillaris, which is the layer of the choroid for blood flow of the outer retina (Garron, 1963; Hogan and Alvarado, 1967; Lerche, 1963). Once established, the RPE aids in

homeostasis, function, and survival of photoreceptor cells. The RPE participates in metabolic transport between the subretinal space and blood, production of cytokines and immunosuppressive factors, and secretion of growth factors, such as brain-derived neurotrophic factor (BDNF), basic fibroblast growth factor (bFGF), glial cell line-derived neurotrophic factor (GDNF), vascular endothelial growth factor (VEGF) and pigment epithelium-derived factor (PEDF) (Dornonville de la Cour, 1993; Falk et al., 2012; Gao and Hollyfield, 1992; Ishida et al., 2003, 1997; Kliffen et al., 1997; Kvanta, 1995; Lopez et al., 1996; Park and Hollenberg, 1989; Schweigerer et al., 1987; Steinberg, 1985; Sternfeld et al., 1989; Streilen et al., 2002; Sugita et al., 2009, 2006; Tombran-Tink et al., 1995; Zamiri et al., 2006).

One of the main tasks of RPE cells is the phagocytic processing of shed outer segments from the distal end of photoreceptors through a daily circadian rhythm (Finnemann, 2003; LaVail, 1976; Ratto et al., 1991; Young and Bok 1969). During differentiation, photoreceptors extend light-sensitive outer segments causing RPE cells to elongate apical microvilli to surround the photoreceptor outer segments. Photoreceptors structurally consist of an inner segment, which contain mitrochondria enabling energy production for the cell, and an outer segment consisting of membranous discs. The outer segment discs are shed from the tips of the outer segment, which are engulfed by the apical microvilli of the RPE cells. This process relies on the polarized distribution of proteins on the RPE, such as $\alpha_v\beta_5$ integrin expression on the apical surface, that are involved in the phagocytic process (Nandrot et al., 2008). The outer segment discs contain opsin proteins and are responsible for the absorption of light. Opsin is generated in the inner segment and transported to the outer segment. Retinal, a product of vitamin A, is transported to the outer segment discs from the RPE cells. Together these components constitute visual pigments and reside within the membranes of the outer segment discs. When light is absorbed, the retinal isomerizes from the 11-*cis*-retinal form to the all-*trans*-retinal form and undergoes conversion to all-*trans*-retinol. During the visual cycle, photoreceptors are unable to convert all- *trans*-retinol back into 11-*cis*-retinal so it is transported to the RPE for reisomerization and recycled back to photoreceptors. Undoubtedly, the RPE plays a major role in the health, stability, and functioning of the photoreceptor cells and the survival of photoreceptors is contingent upon the viability of RPE.

Retinal cell composition differs according to geographic and functional properties. The macula is located at the center of the retina and enables high visual acuity due to a dense cone photoreceptor population (Curcio et al., 1990; Jonas et al., 1992). The peripheral retina has an approximately 20:1 rod to cone photoreceptor ratio, whereas the macula has a 9:1 ratio and a higher ratio (23:1) of cone to RPE cells (Curcio et al., 1990; Gao and Hollyfield, 1992; Snodderly et al., 2002; Young, 1971). To compensate, macular-specific RPE cells have adapted different properties from RPE in the rest of the eye. Macular RPE cells are smaller in diameter, contain more melanin, have a different apical structure, and are better adapted for a higher turnover rate of photoreceptor outer segments (Spitznas and Hogan, 1970; Steinberg et al., 1977; Streeten, 1969; Teirstein et al., 1980; Weiter et al., 1986). The macula is metabolically demanding and receives one of the highest blood flows in the body. It is exposed to high oxygen pressure and experiences photo-oxidative damage making it a target of high levels of reactive oxygen species and other chronic oxidative modifiers that

can activate the immune response (Chou et al., 2008; Ham et al., 1978; Winkler et al., 1999). The imbalance between the production and clearance of damaged cellular components leads to accumulation within and surrounding the RPE, RPE cell dysfunction/loss, and eventual photoreceptor degeneration. The intricacies of retinal cell communication and structure must be maintained for proper visual function, though a number of these mechanisms in both healthy and diseased retina are not well understood.

2. Retinal degenerative diseases (RDDs)

2.1. Age-related macular degeneration (AMD)

2.1.1. Characterization and pathogenesis of AMD—AMD is one of the leading causes of blindness in people over 60 years of age in developed countries and is projected to reach almost 200 and 280 million by 2020 and 2040, respectively (Bird, 2010; Lim et al., 2012; Klein et al., 2011; Wong et al., 2014). One of the confounding aspects of AMD is that it is a multifactorial disease that has both genetic and lifestyle epidemiological factors. Genome-wide association studies (GWAS) have detected a large number of risk variants and loci (Fritsche et al., 2016). Among those identified, the most common variants are in genes of the complement and immune system, while other susceptibility loci implicate a wide range of biological processes such as angiogenesis, lipid metabolism, and extracellular matrix homeostasis (Chen et al., 2010; Edwards et al., 2005; Hageman et al., 2005; Haines et al., 2005; Klein et al, 2005; Maller et al., 2007; Neale et al., 2010; Yu et al., 2011). In addition to genetic components, a variety of environmental risk factors have also been associated with AMD, such as aging, smoking, ethnicity, body mass index, and diet (Klein et al., 1992; Mitchell et al., 1995; Seddon et al., 2003, 2001; Tomany et al., 2004; Vingerling et al., 1995). With so many contributing factors, AMD continues to have one of the most diverse and widespread population of patients.

Historically there have been two clinically recognized forms of AMD, termed dry and wet forms, but more histopathological distinctions have categorized AMD into more detailed classifications (Age-Related Eye Disease Study Research Group, 2000; Haab, 1885). Extracellular deposits, called drusen, form between the inner collagenous layer of the Bruch's membrane and the basal lamina of the RPE (Bird, 1992; Sarks, 1980). The presence of drusen leads to local inflammation caused by oxidative damage, which is thought to initiate AMD progression (Anderson et al., 2002; Hollyfield et al., 2008). Drusen are distinguishable by the characteristics of their edges and composition. Hard drusen are generally small and discrete yellow-white deposits whereas soft drusen are larger, pale-yellow, and dome-shaped in structure. Hard drusen are detected in both aged and AMD individuals, but the presence of soft drusen within the macula is correlated with higher rates of AMD (Ardeljan and Chan, 2013; Buch et al., 2005; Khan et al., 2016; Rudolf et al., 2008). Much of the categorization of AMD is based on the size and distribution of drusen, which can continue to enlarge and cause loss of RPE and photoreceptor cells (Schuman et al., 2009). Drusen are composed of lipids, proteins, and lipofuscin granules, which are non-degradable material that accumulate within postmitotic cells and increases with age (Curcio et al., 2001; Hannover, 1842; Hueck, 1912; Pauleikhoff et al., 1992; Strehler et al., 1959; Wang L et al., 2010; Wolter and Falls, 1962). Lipofuscin granules themselves are composed

of protein, lipids, carbohydrates, and metals (Brunk et al., 2002). Early AMD is characterized by the presence of few medium-sized drusen (Figure 1A) (Age-Related Eye Disease Study Research Group, 2000). With progression of severity, intermediate AMD is identified by the presence of numerous medium-sized drusen, at least one large-sized druse, and geographic atrophy that does not reach the center of the macula (Age-Related Eye Disease Study Research Group, 2000). Geographic atrophy involves progressive degeneration of the RPE, choriocapillaris, and photoreceptors (Lim et al., 2012; Zarbin, 2016). Advanced AMD is the most progressive and is further subdivided into non-neovascular AMD, defined by geographic atrophy to the center of the macula, and neovascular AMD, which includes choroidal neovascularization through the Bruch's membrane to the retina, causing blood leakage and scarring (Figure 1A) (Age-Related Eye Disease Study Research Group, 2000). Progression of disease is visible with the use of fundus biomicroscopy and is used to classify the degree of severity from early to late AMD (Davis et al., 2005).

Similarities exist between AMD and the typical aging process, including the progressive loss of photoreceptors, thickening of the Bruch's membrane, choroidal thinning, and formation of hard drusen (Ardeljan and Chan, 2013). These changes are detected histopathologically, therefore increasing the difficulty in determining AMD-specific mechanisms and outcomes. Progression to a diseased state occurs when aging related changes are exacerbated by other disease-causing factors, such as dysregulation of inflammation or immune responses and other homeostatic processes (Xu et al., 2009). Autoantibodies to the retina have been detected in AMD patients, and generation of biomarker panels may aid in monitoring AMD (Cherepanoff et al., 2006; Lambert et al., 2016; Morohoshi et al., 2012; Patel et al., 2005; Penfold et al., 1990). Drusen contain complement proteins and induce inflammasome activation, underlying the importance of dysregulated immune functions as bioindicators of AMD (Anderson et al., 2001; Doyle et al., 2012; Hollyfield et al., 2008; Mullins et al., 2000). Lipofuscin can form within RPE cells and consist of undigested photoreceptor outer segments, suggesting that there is dysfunctional digestion (Boulton et al., 1989; Feeney-Burns and Eldred, 1983; Katz, 1989; Sarks et al., 1999; Spraul et al., 1999). Lipofuscin can also accumulate when there is a lack of nutritional antioxidants, and the resulting oxidative stress affects phagocytic and autophagic processes (Hayes, 1974; Katz et al., 1978; Ryhanen et al., 2009; Wang et al., 2009). Additionally, mitochondrial damage is increased in RPE of AMD patients, further implicating oxidative stress in AMD (Feher et al., 2006; Karunadharma et al., 2010; Lin et al., 2011; Nordgaard et al., 2008). Untangling the causative versus correlative factors will aid in the development of future therapeutics targeted to specific biological aspects of AMD.

2.1.2. Current therapeutic options for AMD—Presently, there are no cures for AMD; however, a number of therapies have been shown to slow the progression of vision loss and disease pathology. Most of the effective therapies target advanced neovascular AMD, even though only a small percentage (10–15%) of patients progress to this stage (Ferris et al., 1984). Vitamin supplementation can reduce the risk of developing neovascular AMD by approximately 25%, but if the disease progresses then the main treatment for patients with later stages of AMD is intravitreal injections of vascular endothelial growth factor (VEGF)

antagonists (Age-Related Eye Disease Study Research Group, 2001; Age-Related Eye Disease Study 2 Research Group, 2013; Brown et al., 2006; Chew et al., 2013; Heier et al., 2012; Rosenfeld et al., 2006). VEGF regulates angiogenesis and has been shown to induce choroidal neovascularization, and antagonist treatment slows or prevents this process (Okamoto et al., 1997; Tong et al., 2006). The first U.S. Food and Drug Administration (FDA) approved drug for AMD was pegaptanib (Macugen, Pfizer), which targets the VEGF-165 isoform (Gragoudas et al., 2004). Other targeted treatments including ranibizumab (Lucentis, Genentech/Novartis) and bevacizumab (Avastin, Genentech), bind all VEGF-A isoforms and have equivalent efficacy in a head-to-head comparison (Brechner et al., 2011; Brown et al., 2006; Martin et al., 2011; Rosenfeld et al., 2006). Clinical trials have shown that monthly treatment with ranibizumab prevented vision loss in almost 95% of patients and 40% had moderately improved visual function (Rosenfeld et al., 2006). Analysis of VEGF antagonists have shown that legal blindness due to AMD has reduced by 50% (Bloch et al., 2012). Another treatment, aflibercept (VEGF Trap-Eye, Regeneron/Bayer) is an engineered protein that binds VEGF-A, VEGF-B, and placental growth factor (PGF), and has similar efficacy to ranibizumab (Dixon et al., 2009). While VEGF treatments have proven effective for advanced neovascular AMD, patients with early to intermediate AMD have fewer options beyond vitamin supplementation and diet/lifestyle modifications. For end-stage AMD, visual implants are being tested in which the patient receives a miniature telescope to project enlarged images onto the retina (Hudson et al., 2006; Lane and Kuppermann, 2006). Diverse and novel approaches to targeting different stages of AMD will increase the chance that patients will be able to maintain or restore some visual function.

2.2. Retinitis pigmentosa (RP)

2.2.1. Clinical presentation and genetic components of RP—RP is estimated to affect 1 in 4,000 individuals totaling over 2 million individuals wordwide (Sorrentino et al., 2016). The age of onset of RP varies from infancy to late middle age with severe visual impairments detected by age 40–50 (Haim et al., 1992; Parmeggiani, 2011). In early stages of RP, rods degenerate and patients experience night blindness and progressive loss of the peripheral visual field. In later stages of RP, patients develop tunnel vision and eventual cone degeneration leading to severe vision impairment. Approximately 25% of patients become legally blind (20/200) and 0.5% become completely blind in both eyes (Grover et al., 1999). Clinical hallmarks of RP are bone-spicule shaped pigment deposits in the retina, progressive degeneration, attenuated retinal vessels, and optic nerve pallor (Donders, 1857; Landolt, 1872). Typically, the macula is spared until very advanced stages of RP, where macular cysts or perifoveal capillary leakage can occur (Fishman et al., 1977).

RP is a hereditary and genetically heterogeneous with 260 genes and 4,500 mutations identified accounting for less than 50% of RPs, and can be inherited as an autosomal dominant, autosomal recessive, or X-linked trait (Bhattacharya et al., 1984; Farrar et al., 1990; McWilliam et al., 1989; Rosenfeld et al., 1992; Sorrentino et al., 2016). Autosomal recessive inheritance accounts for a majority of RP cases (50–60%), with autosomal dominance (30–40%) and X-linked (5–15%) as lesser contributing modes of inheritance (Bunker et al., 1984; Grondahl, 1987; Narayan et al., 2016; Novak-Laus et al., 2002).

Approximately 45 loci have been identified, which accounts for only about half of all patients (Hartong et al., 2006; Narayan et al., 2016). Mutations causing RP can be found in genes encoding proteins for a variety of cellular processes, including rod phototransduction (e.g. *PDE6A*, *PDE6B*, and *RHO*), vitamin A metabolism (e.g. *ABCA4* and *RPE65*), and phagocytosis (e.g. *MERTK*) (Bowes et al., 1989; Charbel Issa et al., 2009; Farber and Lolley, 1974; Gal et al., 2000; Illing et al., 2002; Mackay et al., 2010; Min et al., 1993; Moiseyev et al., 2005; Pittler and Baehr, 1991; Sung et al., 1993; Weng et al., 1999). Other hereditary retinal disorders can also be attributed to these same genes or cellular processes. Leber congenital amaurosis (LCA) is an inherited retinal dystrophy that causes blindness or severe visual impediments at birth, and similar to RP, can be caused by mutations in *RPE65* (Cremers et al., 2002; Leber 1869; Marlhens et al., 1997). LCA is distinguishable from RP in that the onset of disease is much earlier and patients experience loss of central visual acuity (Cremers et al., 2002; Foxman et al., 1985). Similarly, RPE dysfunction due to mutations in other RPE-specific genes can also cause retinal degeneration. Best disease is a macular dystrophy with childhood onset, and is caused by RPE dysfunction due to mutations in the *BEST1* gene, though the etiology tends to more closely resemble AMD with accumulation of lipofuscin and loss of central visual acuity (Kramer et al., 2000; Marquardt et al., 1998; Petrukhin et al., 1998). Additionally, RP can also be attributable to Usher syndrome (Boughman et al., 1983, Edwards et al., 1998). This disorder is characterized by progressive vision and hearing loss, and can be due to mutations in genes that are important for both the inner ear and photoreceptor cells (Mathur and Yang, 2015).

Regardless of the affected gene, RP vision deficits are due to photoreceptor degeneration through apoptosis, though the mechanisms of action vary (Chang et al., 1993; Frederick et al., 2001; Green et al., 2000; Li et al., 1996; Portera-Cailliau et al., 1994; Sung et al., 1994). Mutations in the rhodopsin gene (*RHO*) account for approximately 30% of all autosomal dominant cases of RP and though a number of mutations are in rod-specific genes, histopathologic examination of patients with advanced stages of RP show degeneration of both rod and cone photoreceptors (Figure 1B) (Berson, 1993; Ferrari et al., 2011; Sohocki et al., 2001). Conversely, mutations in cone-specific genes only lead to loss of cones, suggesting that cone survival is contingent upon rod photoreceptor viability (Cho et al., 2013; Leveillard et al., 2004; Xu et al., 2012; Yang RB et al., 1999; Yang Z et al., 2002). In addition, Müller cells phagocytose shed outer segments from cones and participate in the cone-specific visual cycle, which may also explain why cones evade initial stages of degeneration (Fleisch and Neuhauss, 2010; Long et al., 1986; Muniz et al., 2007). With so many different genes and mechanisms involved, targeting RP may require multiple therapeutic methods.

2.2.2. Current therapeutic strategies for treating RP—No proven treatment exists for a majority of RP patients; however, a range of therapeutic strategies are being tested. Dietary supplementation modestly slows the progression of RP and is recommended by many physicians. A regimen of high doses of docosahexaenoic acid (DHA) from oily fish and vitamin A has been shown to cause a significantly slower decline in cone ERG amplitudes, loss of visual field, and retinal degeneration (Berson et al., 2004, 19934; Gamel and Barr, 1993; Hoffman et al., 2004; Hughbanks-Wheaton et al., 2014). Other clinical

studies have tested pharmacological treatment with oral valproic acid, nilvadipine, and beta-carotene, and may prove effective for incorporation into the current supplementation therapies (Kumar et al., 2014; Nakazawa et al., 2011; Rotenstreich et al., 2013).

Other potential treatments for RP involve surgical interventions. One biomechanical strategy in clinical trials uses retinal prosthetics to act as artificial retinas. A light-sensitive electrode is surgically implanted onto the retina and the patient wears glasses with a mounted camera, which transmits signals to the retinal electrode and these signals are then relayed to the brain. The Argus® II Retinal Stimulation System (Second Sight Medical Products, Sylmar, CA, USA), aptly named after the hundred-eyed giant in Greek mythology, has FDA approval for patients with advanced RP, and has shown improvement in patients' accuracy and repeatability of vision-related tasks (Ahuja et al., 2011; Geruschat et al., 2016; Yue et al., 2015), though a high number of patients (11/30) were shown to have severe adverse effects three years after electrode implantation (Ho et al., 2015). Another route for transplantation strategies is intravitreal delivery of pharmacologics. Certain neurotrophic factors have been postulated to slow the progression of retinal degeneration, but these factors are short-lived proteins that may not traverse the retina in sufficient time to cause an effect. Intravitreal insertion of encapsulated cells secreting neurotrophic factors are being tested, including ciliary neurotrophic factor (CNTF), bFGF, and GDNF (Birch et al., 2013; McGee Sanftner et al., 2001; Tao et al., 2002; Uteza et al., 1999). These neuroprotective factors have been able to slow retinal degeneration in multiple animal models and improve visual acuity in humans (Cayouette et al., 1998; Liang et al., 2001; Sieving et al., 2006; Tao et al., 2002). Discrepancies between morphological rescue and ERG response have been detected with the use of neurotrophic factor treatment in animals, suggesting that many of the neuroprotective mechanisms in the retina are not well understood (Gargini et al., 1999; Lau et al., 2000; Liang et al., 2001). Lastly, the use of gene therapy to target specific patient mutations has been utilized in the rare retinal dystrophy LCA, which contains mutations found in the *RPE65* gene (Marlhens et al., 1997). Using animal models of LCA, subretinal injections of adeno-associated virus (AAV) mediated *RPE65* gene delivery was able to restore vision (Acland et al., 2005, 2001; Bennicelli et al., 2008). In clinical trials, LCA patients also had improved visual ability, and multiple administrations to the same patient were declared safe; however, continue photoreceptor loss is not prevented in some patients (Ashtari et al., 2011; Bennett et al., 2016, 2012; Cideciyan et al., 2013). The backdrop of these seminal gene therapy trials and the pervading use of the CRISPR/Cas9 system (Bakondi et al., 2016; Suzuki et al., 2016; Wu et al., 2016) will allow gene therapy studies and personalized medicine to treat more patients with RP and other retinal degenerative diseases, yet with so many gene variants, targeting individual patients or genes may not be the most efficient route. Other more universal approaches may be needed to target patients with unknown gene mutations or larger patient populations in whole.

3. Cell-based therapeutic strategies for RDDs

3.1. Animal modeling of RDDs

For a number of diseases, animal models do not depict a direct manifestation of what occurs in human patients. Different species are selected for specific disease studies based on their

anatomical features or genetic background (refer to reviews by Pennesi et al., 2012; Rivas and Vecino, 2009; Zarbin, 2016; Zeiss, 2010). Considering AMD is a multifactorial disease with both genetic and environmental contributions, it has proven difficult to develop a comparable animal model. While some of the genetic mutations found in AMD patients have been studied in animals, environmental factors cannot be as easily replicated (Espinosa-Heidmann et al., 2006; Fujihara et al., 2008; Zeiss, 2010). Additionally, aging is one of the most influential attributes for the disease, and the aging process is not comparable between humans and other species, as both the human lifespan and the regulation of biological processes of aging are different from mice and nonhuman primates (Fraser et al., 2005; Khaitovich et al., 2004; Kim, 2007; Klein et al., 1992; Mitchell et al., 1995; Vingerling et al., 1995; Zijlmans et al., 1997). The anatomical features of the eye also differ between species. The macula is responsible for high-acuity vision and is only found in primates and some birds and reptiles, meaning that the most utilized species of vision research do not have the main anatomical feature of study.

Unlike AMD, RP is typically a monogenic disease, and developing and identifying animal models which mimic the human disorder has been more direct. Animal models of RP can occur through transgenic manipulations or naturally occurring mutations and many of the same genes are found in mutated animals as humans (Rivas and Vecino, 2009). The fault with transgenic technology is that the transgene is added to a wild-type background and does not accurately represent the human mutation. While these forms of animal models can lead to retinal degeneration and other pathogeneses of RP, it should be taken into account that this is not an exact representation of the human condition (Redmond et al., 1998). Naturally occurring mutations leading to retinal degeneration have been detected in animals and are used for modeling RP (Chang et al., 2007; Keeler, 1966; Pang et al., 2005). Spontaneous models are more direct as they possess a number of the same mutated genes as patients with RP, and the benefit is that the mutated gene directly leads to retinal degeneration and is not an indirect effect of transgene interference. The reoccurring theme with animal modeling is that there is no perfect representation, but information extrapolated from each of the models will hopefully contribute to a broader knowledge of retinal degeneration and the best tactic for treatment.

3.1.1. Mouse models of retinal degeneration—Both mice and rats are inexpensive models for biomedical research, and each has added benefits that make it preferred over the other species. Mice are genetically easy to manipulate to express mutations mimicking those identified in human AMD or RP. For AMD, one of the first gene mutations discovered in humans was in the complement factor H (*CFH*) gene, and the $Cfh^{-/-}$ mouse has similar disease features including loss of photoreceptors, reduced rod function, and complement deposits; however, these animals also experience complications with glomerulonephritis and can die prior to any retinal malformations (Coffey et al., 2007; Edwards et al., 2005; Haines et al., 2005; Pickering et al., 2002). In addition to *CFH*, a number of the mutations in mice affect the immune response and have AMD-like pathology or dysregulated lipid metabolism and oxidative stress similar to the human condition (Ambati et al., 2003; Combadiere et al., 2007; Cousins et al., 2002; Dithmar et al., 2000; Heckenlively et al., 2003; Imamura et al., 2006; Luhmann et al., 2009; Rudolf et al., 2005; Tuo et al., 2007; Zhao et al., 2011). Genetic

mouse models of Stargardt macular dystrophy, a juvenile form of macular degeneration, have also been utilized for AMD studies. Mutations in the *ABCA4* gene can cause either Stargardt macular dystrophy or AMD, and Abca4 knockout mice accumulate lipofuscin granules, causing eventual degeneration of RPE and photoreceptors (Allikmets et al., 1997a, 1997b; Mata et al., 2000; Shroyer et al., 2001; Weng et al., 1999). Similarly, *ELOVL4* mutations identified in Stargardt and AMD patients, and Elovl4 transgenic mice develop lipofuscin granules (Ayyagari et al., 2001; Karan et al., 2005). Common mutations in multiple forms of macular degeneration, such as Stargardt and AMD, allows for therapeutic discoveries to be used for multiple diseases.

Naturally occurring mutations in mice have been identified and are used as models of different modes of inheritance of RP. Naturally occurring mutations in the cGMP phosphodiesterase subunit 6β (PDE6β) causes autosomal dominant RP (Q334ter mouse) or autosomal recessive RP (rd1 and rd10 mice) with varying rates of degeneration (Chang et al., 2007; Frasson et al., 1999; Jimenez et al., 1996; McLaughlin et al., 1993; Sung et al., 1994). The transgenic models also cover the spectrum of inheritance patterns in RP. Transgenic mice expressing the Pro23His (P23H) mutation in rhodopsin exhibit photoreceptor degeneration and a decrease in rod-mediated ERG response at one month of age (Goto et al., 1995; Lewin et al., 2014; Olsson et al., 1992). Autosomal recessive RP is modeled in Rpe65 knockout mice, which have no loss of rod photoreceptors until 6 months of age but do exhibit cone degeneration at 2 to 3 weeks after birth (Redmond et al., 1998; Rohrer et al., 2003; Seeliger et al., 2001; Van Hooser et al., 2000; Znoiko et al., 2005). The availability of numerous mouse models allows for diverse studies based on the modes of inheritance, gene of interest, and rate of degeneration.

3.1.2. Rat models of retinal degeneration—Though genetic manipulations are not as easily replicated in rats, there are many benefits over mice in laboratory studies. Rats are the most commonly used animal for biomedical studies and were the first animal domesticated for scientific research, therefore their physiology and biological systems have been extensively studied (Sengupta, 2013). Rats are larger than mice allowing for easier handling and surgical procedures, and the benefit of using rats in vision research is that the rat eye is 6 mm in diameter and approximately twice the size of the mouse eye (Hughes, 1979; Massof and Chang, 1972; Remtulla and Hallet, 1985). One of the most commonly utilized animal models for retinal degeneration is the Royal College of Surgeons (RCS) rat, which contains a mutation in the Mertk gene (D'Cruz et al., 2000; Vollrath et al., 2001). As *MERTK* mutations are also found in patients with RP, RCS rats are used as a general model for inherited retinal degeneration due to RPE dysfunction (Charbel Issa et al., 2009; Mackay et al., 2010). The *Mertk* gene encodes for a tyrosine kinase receptor mainly expressed in RPE cells and mediates proper phagocytosis of shed photoreceptor outer segments (D'Cruz et al., 2000). The mutation causes a premature stop codon which translates to a truncated protein, therefore, RPE cells have an inability to properly phagocytize shed photoreceptor outer segments and debris accumulates between the photoreceptors and RPE and leads to photoreceptor loss in the third postnatal week of age (Bok and Hall, 1971; Dowling and Sidman, 1962; Herron et al., 1969; LaVail 1981; Vollrath et al., 2001). In an effort to further the use of RCS rats, an immune-deficient RCS strain was recently developed, which may

negate the use of immunosuppressants in transplantation studies (Thomas et al., 2016). While RCS rats are extensively used in preclinical studies, some caution should be heeded. One concern is that sham surgery containing only cell-carrying media causes some increase in visual response, potentially by clearing debris from the subretinal space and trophic support induced by surgical injury; however the effect diminishes over time (Cao et al., 2001; Sauve et al., 2002; Wen et al., 1995). Human RPE cell lines transplanted into the subretinal space of RCS rats had photoreceptor rescue distal to the injection site, suggesting that some of the rescue was due to a trophic effect (Lund et al., 2001). In addition, a majority of studies perform cell injections at an early age, typically age P21–30. At this age, unlike AMD patients, RCS rats have a young Bruch's membrane which may not represent similar conditions in aged patients with AMD for transplantation studies. RCS rats have been used extensively in both AMD and RP research and remain as one of the most utilized animal models for preclinical studies on retinal degeneration. Similar pathogenesis in various retinal degenerative diseases allows for the crossover use of animal models, thus enabling a broader knowledge of the mechanisms of disease.

Though RCS is the most utilized, other rat models mimic the pathology and progression of retinal degeneration. For studying AMD, the OXYS rat spontaneously develops a phenotype similar to human aging and AMD-like pathology, including drusen formation, associated with immune and inflammatory responses (Kozhevnikova et al., 2013; Markovets et al., 2011; Zhdankina et al., 2008). For studying RP, transgenic rat models for *RHO* have been developed. Transgenic P23H rats, similar to the P23H mouse, have progressive loss of rod photoreceptors starting at age P21 and abnormal rod ERG response at 4 weeks of age (Cuenca et al., 2004; Lu et al., 2013; Machida et al., 2000). S334ter rats carry mutations that cause truncated rhodopsin, and different transgenic lines of this rat model develop different rates of degeneration (Green et al., 2000; Steinberg et al., 1996). Heterozygous S334ter line 3 rats undergo rapid photoreceptor degeneration, with greater than 50% of the photoreceptor death by age P11–12 (Liu et al., 1999; Martinez-Navarrete et al., 2011). Conversely, heterozygous S334ter line 4 rats develop slower degeneration and have 8 to 10 layers of photoreceptor cell bodies within the outer nuclear layer at P15 and degeneration occurs until age P60 (McGee Sanftner et al., 2001). An immunodeficient S334ter rat strain was developed for xenogeneic transplantation studies without the need for immunosuppressants (Seiler et al., 2014). Though rat models do not accurately portray the human disease or anatomy, rats are generally regarded as the optimal model due to the ease of handling and surgery, cost-effective husbandry, and range of functional tests that can be performed.

3.1.3. Large animal models of retinal degeneration—Larger animal models, such as rabbits, pigs, dogs, and nonhuman primates, have eye diameters more similar to the human eye size allowing for comparable surgical tools and techniques, and yet vascular and retinal anatomy differs between the species (Bekerman et al., 2014; Beltran 2009; De Schaepdrijver et al., 1989; Harding et al. 2013; Hayreh 1996; Hughes et al., 1972; Lapuerta and Schein, 1995; Olver, et al. 1994; Sanchez et al., 2011;Ueno et al., 2013). A number of large animal models have been developed; however, only models used in preclinical studies with stem cells will be summarized in this review.

The most anatomically similar organisms to humans are nonhuman primates, but are costly to maintain and have ethical concerns with the close evolutionary relationship to humans (Varki and Altheide, 2005). Spontaneous AMD models have been discovered with varying AMD-like pathology. Drusen and pigment changes akin to early to intermediate AMD have been detected in aged rhesus macaque monkeys (*Macaca mulatta*) and drusen are structurally and compositionally similar to human drusen (Bellhorn et al., 1981; Dawson et al., 1989; El-Mofty et al., 1980; Gouras et al., 2008; Hope et al., 1992; Olin et al., 1995; Stafford et al., 1984). Susceptibility genes and variants are shared with humans, indicating conservation of pathogenetic mechanisms between human and nonhuman primates (Francis et al., 2008; Singh et al., 2009). Similar AMD-like symptoms, including RPE atrophy and complement deposition, were found in the cynomolgus macaque (*Macaca fascicularis*) and the Japanese macaque (*Macaca fuscata*), suggesting that some of the pathogenic mechanisms are common (Neuringer et al., 2010; Nicolas et al., 1996; Suzuki et al., 2003; Umeda et al., 2005a, 2005b). The presence of a macula in nonhuman primates allows for closer relevance to humans, yet housing, maintenance, and a large sample size for preclinical studies is not always feasible, cost-effective, or justifiable for long-term studies of AMD.

Genetic engineering in pigs has developed multiple models for studying RP. The pig eye is comparable in size to the human, and contains a cone-dense visual streak considered analogous to the macula (De Scaepdrijver et al., 1990; Sanchez et al., 2011). Additionally, ophthalmic diagnostics, such as OCT and ERG, can be used on the pig eye without much adaptation from the human parameters (Maverick et al., 2004; Van Velthoven et al., 2004). A transgenic pig with a rhodopsin mutation (Pro347Leu) has similar degeneration to RP in humans with rod cells normal at birth but with short outer segments leading to early rod cell death (Berson et al., 1991; Dryja et al., 1990; Li et al., 1998; Petters et al., 1997; Tso et al., 1997). At 20 months, the pigs have abnormal cone morphology and cone ERG (Petters et al., 1997). A similar model, the P347S transgenic pig, has a slower rate of degeneration, but few studies have utilized this model (Kraft et al., 2005; Shaw et al., 2001). P23H transgenic pigs model autosomal dominant RP and have a clinical phenotype similar to RP patients, including a reduced ERG (Ross et al., 2012). This model has been used to develop intraocular surgical techniques for clinical application. More commonly, studies utilize pigs for testing surgical feasibility rather than efficacy of treatment. The limiting factor in the use of pigs is the cost and maintenance of the animals as not many facilities are equipped for the care of pigs, nor do many researchers have the funds with which to use them.

3.2. Stem cells and the clinical potential for RDDs

The discovery of stem cells is arguably one of the greatest and most promising areas of biomedical research. Human embryonic stem cells (ESCs) and their less ethically controversial counterpart, induced pluripotent stem cells (iPSCs), have the ability to self-renew, thus generating a potentially inexhaustible line of cells that can be used for testing, treatment, and transplantation (Takahashi et al., 2007; Thomson et al., 1998). Government and public policy has shaped funding and the general opinion of stem cell-specific research. Public polls indicate a preference for the use of iPSCs rather than ESCs in research, yet the understanding is that there is a necessity for regenerative medicine with proper regulations (Critchley et al., 2013; Shineha et al., 2010). The benefits of stem cells extend beyond the

direct effects as therapeutics and into platforms for drug and toxicology screening, and iPSCs allow for disease- or patient-specific modeling and personalized medicine (see Singh et al., 2015 for a review). These advancements have enabled a number of the first stem cell clinical trials targeted to vision disorders. This review will summarize the preclinical and clinical studies utilizing cell-based therapies with a focus on the retinal degenerative diseases AMD and RP. Two prevailing applications of cell therapies will be highlighted. The first utilizes stem cell differentiation into RPE cells for replacement of defective or dying endogenous RPE cells. The second approach is to exploit cells as a support system for preservation of photoreceptors and visual function. Additionally, the remaining obstacles that need to be overcome to ensure the use of cell-based therapies in future clinical practices will be discussed. With the growing number of clinical trials using cell therapies for vision disorders, progress over the next five to ten years will dictate their use for the future.

3.2.1. Considerations for an ideal cell source for treatments—For cell-derived therapies to become standard regimens of care, a number of considerations must be met to allow efficient therapeutic use and value. From the research and bench side aspects, cells would need to be easily propagated and maintained as cell culturing can be labor intensive, time-consuming, and utilize costly reagents. From a biological standpoint, derivation and differentiation protocols would need to be optimized for efficient and reproducible cell lines for large scale production and universal cell donor banks would negate some of the necessity of multiple, repetitive cell lines. From a health and welfare perspective, the cells would need to be highly efficacious with no tumor formation or other adverse effects. Autologous cell derivation would be optimal for most therapies because the least immunologic response would be from cells derived from the same patient, barring any disease-causing mutations that need to be addressed prior to transplantation. As cell-based therapies for ocular disorders becomes more common, clinicians and support staff would need to be trained in handling stem cells, which may have different specifications than organ transplants. Finding and utilizing a cell source that suitably addresses all of these concerns will be difficult, and there may prove to be multiple strategies and types of cells that would adequately meet these guidelines.

3.2.2. Targeted patient population for cell-based therapies—Patients that would benefit from either RPE replacement or cell-based preservation strategies require similar criteria. Most importantly, the status of disease progression will dictate how well the host retinal tissue will respond to the transplant. Events preceding the loss of photoreceptor cells, such as changes in the choriocapillaris and RPE, can have long-term implications for disease progression and treatment. Changes in the choroid, including the density and thickness of the choriocapillaris, and Bruch’s membrane have been detected in patients with AMD, which may alter the potential of transplanted cells for either engraftment or restorative effects (Almeida et al., 2015; Chung et al., 2011; Spraul et al., 1996; Whitmore et al., 2015). One of the main components of AMD is diseased RPE; therefore, the idea of replacement therapy is to take exogenous RPE cells for transplantation into a patient that has lost their own. The goal of this treatment would be to replace or supplement the existing non-functional and dying RPE cells with new, healthy RPE cells, which will hopefully take over the roles that are needed for visual function. If replacement is performed too soon, then the

host RPE cells may still occupy the Bruch's membrane and not allow the engraftment and functionality of new RPE cells. This would not be a complication in later stages of disease as dead RPE cells would become detached from the Bruch's membrane; however, if replacement treatment is performed after all of the RPE cells are gone then there may be limited photoreceptor cells remaining. Photoreceptors may be able to survive after loss of RPE cells, but the codependency of RPE and photoreceptor cell survival will be compromised (Longbottom, et al., 2009; Zieger and Punzo, 2016). Patients will need to have a sufficient number of surviving, functional photoreceptor cells otherwise replacing RPE cells will be not be worthwhile for the task of rescuing vision. An appreciable amount of photoreceptor cells will also be necessary for cell-based preservation strategies. The goal of preservation is to transplant cells that are able to support long-term retinal structure and function. Preservation strategies do not aim to replace any dead or dying endogenous cells, yet the transplanted cells are able to halt the progression of disease. Supportive cells potentially function by secreting neuroprotective factors that are able to aid in photoreceptor survival, thus preserving visual function. Similar to RPE replacement strategies, transplantation of supportive cells will only be efficacious if there are sufficient photoreceptor cells remaining and retinal remodeling due to degeneration is not at advance stage (Jones et al., 2016). One concern is that retinal degeneration may reach a point of no return, implying that photoreceptor damage comes to a stage at which no intervention can save or preserve the cells. Intervention after the onset of substantial photoreceptor loss has not been able to change the course of degeneration or restore visual function, suggesting that the interventional timing is paramount to maximal efficacy, which may differ on a patient- or disease-specific basis (Cideciyan et al., 2013).

RPE replacement strategies are currently targeted for patients with AMD or Stargardt macular dystrophy; whereas preservation therapies are designed for either AMD or RP patients, though more knowledge of the extent of efficacy and mechanisms in these cellular therapies could broaden the patient population to potentially include other retinal degenerative disorders. One advantage to preservation strategies is that the transplantation of allogeneic cells is gene- and mutation- independent. AMD has multiple gene and epidemiological risk factors, and RP has numerous risk variants and loci, which complicates the generation of universal treatments (Fritsche et al., 2016; Sorrentino et al., 2016; Tomany et al., 2004). Supportive cells for preservation techniques are designed to encompass diseases with an array of mutations and risk factors, and could potentially treat a large population of patients. Nonetheless, in order to generate the most benefits from any cell-based therapy, identification of a specific patient population must meet certain criteria for efficacy.

3.3. Replacement therapy using RPE cells

3.3.1. RPE cell sources—Studies using exogenous RPE sources have paved the way for stem cell-based replacement therapies. The first demonstration of RPE cell replacement in a defective RPE environment used wild-type Long Evans rat RPE transplanted into the RCS rat with cell survival up to one year after transplantation and photoreceptor preservation, suggesting that exogenous RPE cells can be grafted and survive in a diseased environment (Li and Turner, 1991, 1988). In humans, translocation studies of autologous RPE cells have

shown that adult, mature RPE from the retinal periphery could be transplanted to other areas of the eye with graft survival, yet varying results in visual acuity and adverse effects from surgery constrict the use of grafted whole tissue (Binder et al., 2002; Gouras et al., 1985, 1983; Heussen et al., 2008; Lane et al., 1989; Peyman et al., 1991). Adult RPE cells can be cultured and grown as monolayers and exhibit typical RPE characteristics *in vitro*, suggesting that RPE cells are able to maintain their native state in different environments (Blenkinsop et al., 2015, 2013). Despite these characteristics, difficulties with culturing primary RPE cells restrict their potential use. One example is that these cells have a relatively short shelf-life as there is a limited passaging potential in culture (about 4 to 8 passages) thought to be due to phenotypic instability and senescence-induced loss of RPE characteristics (Bharti et al., 2011; Klimanskaya et al., 2004; Singh et al., 2013). These limitations indicate a need for more stable RPE cells that can be stored and utilized at will for transplantation treatments, such as ESC- and/or iPSC-derived lines.

The derivation of ESC- and iPSC-RPE has commonalities, but each cell source has its own added benefits and disadvantages. It should be noted that further discussions of ESC- or iPSC-RPE are human in origin unless otherwise described. Two main approaches are used for the generation of RPE or RPE-like cells from stem cells. In spontaneous differentiation, cells are overgrown as adherent cultures, and these embryoid bodies form pigmented cells that can be further plated (Klimanskaya et al., 2004; Lund et al., 2006; Meyer et al., 2009; Vugler et al., 2008). These protocols are lengthy at approximately 30 to 50 days, and yet the timing and efficiency can be highly variable (Lane et al., 2014). In directed differentiation, specific factors are added to the culture media to mimic the developmental process and induce RPE differentiation (Buchholz et al., 2013; Idelson et al., 2009). This process can also take several weeks and techniques may be lab preferential (Idelson et al., 2009). Comparisons of spontaneous and directed differentiation protocols detected that some iPSC lines are not amenable to spontaneous differentiation, and differences exist with transcript levels of RPE-specific expression between iPSC lines (Leach et al., 2016). In addition, RPE cells can be transplanted as single cell suspensions or as monolayers seeded on scaffolds (Figure 2A). Continual improvements and optimizations are made to protocols; however, there are no standardized or regulated modes of RPE derivation.

ESC lines could act as universal donors for a large population since these cells are generally not immunogenic. Limited expression of major histocompatibility complex (MHC) class I molecules and no expression of MHC class II molecules have been detected, thus reducing the possibility for rejection (Drukker et al., 2006; Suarez-Alvarez et al., 2010). ESC-RPE has gene expression profiles similar to mature RPE cells, and protein expression includes those involved in retinol cycling (Figure 2B) (Klimanskaya et al., 2004; Liu et al., 2014; Peng et al., 2013). ESC-RPE is morphologically and functionally similar to native RPE cells and grow as a monolayer of characteristically pigmented, hexagonal shaped cells (Figure 2C and C'), form microvilli, and perform phagocytosis of rod outer segments (Carr et al., 2009b; Idelson et al., 2009; Vugler et al., 2008). Correct apical-basal polarity has been described with polarized-specific protein expression and growth factor secretion (Vugler et al., 2008; Zhu et al., 2011). ESC-RPE appear to function and behave as typical RPE cells, though variability in cell maturity *in vitro* may require further classification to ensure pure populations of appropriate cells for transplantation (Lu et al., 2009).

In addition to allogeneic cell sources, iPSC-RPE would allow for autologous transplantation of cells, thereby negating any discrepancies in immune-related compatibility for the patient. Similar to ESCs, iPSCs also have low MHC class I and no MHC class II expression and share morphological and functional properties akin to native RPE cells (Suarez-Alvarez et al., 2010). iPSC-RPE cells are pigmented and hexagonal in shape, express characteristic visual cycle proteins (e.g. RPE65, lecithin retinol acyltransferase (LRAT), and cellular retinaldehyde-binding protein (CRALBP)), have apical microvilli, and secrete VEGF-A (Brandl et al., 2014; Hirami et al., 2009; Muniz et al., 2014; Singh et al., 2013). The gene expression profiles are similar to ESC-RPE; however, iPSCs may retain epigenetic markers of their cell of origin (Buchholz et al., 2009; Kim et al., 2010). Due to these epigenetic artifacts, iPSC-RPE may be more efficiently produced from retinal lineage cells than fibroblasts, yet this would require patient retinal biopsies or fetal retinal sources (Hiler et al., 2015; Hu et al., 2010). Transdifferentiation protocols for direct differentiation from fibroblasts to RPE cells would bypass the step of inducing pluripotency, potentially decreasing the time and handling in culture (Zhang et al., 2013). Some of the disadvantages of iPSCs are analogous to ESCs, such as low efficiency of conversion to RPE and diversity between different cell lines (Buchholz et al., 2009). Whether ESC- or iPSC-RPE cells are used, all of these factors must be taken into consideration by each study and trial to anticipate any complications that may arise.

3.3.2. Preclinical studies and clinical trials using stem cell-derived RPE cells—

The ability of ESC-RPE cells to rescue visual function was first demonstrated using primate cells grown as RPE monolayers transplanted into RCS rats (Haruta et al., 2004). Human ESC-RPE was then injected into RCS rats and Elovl4 mice and was also shown to have preservation of visual function and less photoreceptor degeneration with no teratoma formation in immune-deficient mice (Lu et al., 2009; Lund et al., 2006; Vugler et al., 2008). These preclinical studies have laid the foundation that the transplantation of ESC-RPE into degenerate retinas is feasible and that the cells are able to survive and provide a benefit to photoreceptor cells and visual function. This review will summarize clinical trials with published outcomes, but for a complete list of current clinical trials please refer to Table.

The use of ESC-RPE cells for dry AMD was studied in a clinical trial in the United States originally sponsored by Advanced Cell Technology (formally changed to Ocata Therapeutics, and acquired by Astellas Pharma Inc.) and focused on the safety of subretinal transplantation of ESC-RPE, named MA09-RPE (NCT01344993). Two other ongoing clinical trials by Astellas Pharma Inc. with the use of MA09-RPE cells for dry AMD are also evaluating safety and potential efficacy (NCT02463344 and NCT02563782). Preclinical studies showed that the differentiation of ESCs into RPE cells results in greater than 99% purity and that the MA09-RPE cells had typical RPE behavior, aided in visual function (Figure 2D), and formed monolayers after transplantation into animals (Figures 2E, E’, and E’’) (Lu et al., 2009, Lund et al., 2006). The cells showed no signs of hyperproliferation or immune-mediated rejection in two patients with dry AMD, and one patient had improvements in vision (Schwartz et al., 2012). In a follow-up study, eighteen patients with Stargardt macular dystrophy or atrophic AMD received the MA09-RPE cells in differing cell doses (50k, 100k, and 150k) with no serious adverse effects due to the cells themselves, and

visual acuity improved or remained stable in all but one eye (Schwartz et al., 2015b). This was the first medium- to long-term study of the safety and functionality of ESC-RPE cells in humans. The same MA09-RPE cells were licensed to CHABiotech Co. for a Phase I/IIa clinical trial in the Republic of Korea for testing safety (NCT01674829). Four patients with dry AMD or Stargardt macular dystrophy received subretinal transplantation of the MA09-RPE cells and were followed for one year. No adverse proliferation, tumorigenicity, or other safety issues were detected (Song et al., 2015). Another tactic for replacement therapy for growth RPE cells on a scaffold prior to transplantation. In the United States, Regenerative Patch Technologies has a Phase I/IIa clinical trial for dry AMD on the safety and efficacy of subretinal transplantation of ESC-RPE seeded on an ultrathin polymeric parylene-C scaffold, termed CPCB-RPE1 (NCT02590692). Preclinical studies focused on the subretinal transplantation of CPCB-RPE1 into the Yucatan mini pig and analysis was performed at three months after implantation (Brant Fernandes et al., 2016). The CPCB-RPE1 implants survived, and the ESC-RPE cells still formed an intact monolayer (Brant Fernandes et al., 2016; Koss et al., 2016). No intraocular or systemic tumors were detected, but normal retinal lamination around injection site was disrupted. This study showed that the surgery needs to be improved, and outcomes from the clinical trial will determine the safety and efficacy in humans. In the United Kingdom, Pfizer and the University College London are sponsoring a Phase I clinical trial for the use of ESC-RPE seeded as a monolayer on a polyester membrane, named the Pf-05206388 implant (NCT01691261). In August 2015, the first patient received the implant and has a projected primary completion date of early 2017. These initial trials mainly focus on the safety of ESC-RPE transplantation, but the secondary outcomes measuring efficacy will need to be further evaluated in later phase trials with more patients.

The use of iPSC-RPE in replacement therapies would allow for autologous transplantation, but preclinical studies have had varied outcomes on the immune response to autologous versus allogeneic iPSC-RPE cells. Allogeneic porcine iPSC-RPE were delivered by subretinal injection into Yucatan mini pigs, and while no tumor formation was detected, there was an innate immune response, suggesting that immunologically matched cells may need to be used (Sohn et al., 2015). Similarly, transplant rejection was detected in allogeneic iPSC-RPE sheet transplantation into nonhuman primates, which was not detected in autologous nonhuman primate injections (Kamao et al., 2014). The caveat to these studies is that the iPSC-RPE cells were injected into healthy tissues, and similar immune responses may not be replicated in the diseased environment. Human iPSC-RPE had functional and anatomical rescue of photoreceptors when subretinally injected as xenogenic transplants into retinal degenerate RCS rats (Carr et al., 2009a; Krohne et al., 2012). iPSC-RPE resembled human fetal RPE by proteomic analysis and were able to phagocytose photoreceptor outer segments *in vivo*, yet iPSC-RPE cells survived for longer than the host tissue photoreceptors, suggesting that RPE transplantation alone may not provide lifelong rescue (Krohne et al., 2012; Westenskow et al., 2016). Only one clinical trial has been attempted using iPSC-RPE in humans. In Japan, the RIKEN Institute has a Phase I clinical trial testing autologous iPSC-RPE for wet AMD. In 2014, one patient was successfully transplanted with an autologous iPSC-RPE sheet with no complications from surgery. At a one year follow-up, the graft was viable, visual acuity stabilized, and no tumorigenesis or other abnormalities

were detected (RIKEN, 2015). The trial was on hold for approximately one year due to regulatory changes in Japanese laws. In addition, genomic changes were detected in the cells, and it is unclear if these changes occurred during or prior to the reprogramming process (Garber, 2015). Recently, the trial was able to resume but will continue with allogeneic iPSCs, potentially from an iPSC bank. While the use of autologous cells would negate concerns over immunogenicity, any issues associated with the reprogramming and derivation process would be perpetual concerns with each patient-derived line, thus the feasibility of autologous cell transplants comes into question. With various trials and techniques in progress, the remaining concerns with the use of stem cell-derived RPE will hopefully be elucidated in the coming years as results from the current clinical trials are reported.

3.4. Preservation of photoreceptor cells and visual function via support cells

3.4.1. Cell types for transplantation—The aim of replacement therapies is to replenish the defective or dying RPE cells with new, functional RPE, but the progression of disease must be severe enough that there is room to accommodate exogenous RPE cells on the Bruch's membrane. Unlike AMD, many mutations causing RP directly affect photoreceptor cells themselves, and an alternative strategy for treatment is to try and preserve the remaining vision by halting or slowing the progression of photoreceptor loss, therefore the goal of preservation therapies is to inject supportive cells that are able to aid in photoreceptor survival. Unlike replacement therapies, injected cells will not become or take over the tasks of RPE cells but rather will aid in the survival, stability, and function of photoreceptors. There are numerous types of cells that are used for testing in retinal degenerative diseases; however, this review will focus on cells that are currently being studied in clinical trials.

Mesenchymal stem cells (MSCs) are multipotent cells that can be isolated from a number of tissues, including bone marrow and umbilical cord blood (Gnecchi and Melo, 2009; McElreavey et al., 1991; Pittenger et al., 1999; Stappenbeck and Miyoshi, 2009). MSCs are identified by three main classifications, which include plasticity, expression of specific surface antigens (e.g. CD29, CD44, and CD105), and multipotency (Boucher, 2011; Dominici et al., 2006; Halfon et al., 2011). Endogenous adult MSCs aid in tissue repair and regeneration and can cause immunomodulatory effects, making MSCs attractive as a therapeutic for retinal degeneration (Maitra et al., 2004; Ren et al., 2008). Two specific MSC sources have been utilized in cell therapies for retinal diseases. Umbilical cord-derived MSCs (UC-MSCs) are found in umbilical cord blood/tissue following delivery, cause no risk to the mother or baby donor during collection, and are typically discarded, thus bypassing some of the ethical issues with other stem cell sources (Kurtzberg et al., 2005; Nagamura-Inoue and He, 2014). UC-MSCs can be expanded for several passages *ex vivo* and can be cryopreserved for future use (Kurtzberg et al., 2005; Lund et al., 2007; Sarugaser et al., 2005). Conversely, bone marrow-derived stem cells (BM-MSCs) are adult stem cells acquired through bone marrow aspiration that constitute a small percentage (0.001 to 0.01%) of cells collected, and proliferation is affected by age of the donor (Baksh et al., 2007; Mareschi et al., 2006; Mueller and Glowacki, 2001; Pittenger et al., 1999). Though the benefit of using BM-MSCs is for autologous transplantation, UC-MSCs have a faster

proliferative capacity and the gene expression profile is similar to ESCs (Fong et al., 2011; Hsieh et al., 2010). The use of UC- or BM-MSCs may be contingent upon the most benefit for the patient and disease of treatment, and different sources of MSCs may have varying abilities for retinal preservation. For MSC studies for retinal degeneration, intervention can occur via subretinal injection, intravitreal injection, or systemic administration. Subretinal injection of MSCs allows for direct contact to retinal cells (Figure 3A), but the injection itself can cause damage to the retina. Intravitreal administration still allows for a local injection and reduces damage to the retina, and while the inner limiting membrane can block migration of MSCs, secreted factors from the MSCs may still reach the retina. Systemic administration may only have distal immunomodulatory or neurotrophic effects, as there is limited direct contact with the retina. The major limitation of MSC transplantation is that the grafted cells have short-term survival. Under certain circumstances, MSCs are able to differentiate into retinal cells, but only a small percentage are able to do so *in vivo*, and more commonly, MSCs have a neurotrophic effect on photoreceptor survival (Arnhold et al., 2006; Gong et al., 2008; Inoue et al., 2007; Park et al., 2016; Tomita et al., 2002; Wang S et al., 2010; Zhang and Wang, 2010). MSCs secrete neurotrophic and pro-survival factors, such as CNTF, bFGF, and GDNF, and possess immunosuppressive characteristics, and combined with their self-renewal potential, qualify as an advantageous cell source for preservation therapies (Chen et al., 2011; Lu et al., 2010; Paczkowska et al., 2016; Siniscalco et al., 2010; Yu et al., 2006).

Another group of supportive cell types for preservation studies are nervous system-derived stem and progenitor cells. The difference between stem and progenitor cells is generally thought to be due to the lifespan of the cell. Stem cells replicate indefinitely, whereas progenitor cells are the early descendants of stem cells and have a limited proliferative capacity (Seaberg and van der Kooy, 2003). Another main distinction is the potentiality, as progenitors are more limiting in the types of cells they can derive. One group of cells utilized in preservation therapies is retinal stem/progenitor cells (RSCs/RPCs). RSCs/RPCs are derived during early development and can be isolated, expanded, and differentiate into all retinal cell types *in vitro*; however, a limited proliferative potential and difficulty in securing tissue prevents the expanded use of primary RSC/RPC sources (Angenieux et al., 2006; Chacko et al., 2000; Coles et al., 2004; Kelley, et al., 1995; Klassen et al., 2004; Merhi-Soussi et al., 2006; Yang et al., 2002). Alternatively, RSCs/RPCs can be derived from fetal neural retina, ESCs, or iPSCs, can be expanded through multiple passages, remain in an undifferentiated state, and have a gene expression profile similar to fetal RPCs (Baranov et al., 2013; Ikeda et al., 2005; Lamba et al., 2006; Luo et al., 2014; Qu et al., 2015). RSCs/RPCs have been detected to express photoreceptor proteins and integrate within the host retina, but it is unknown to what extent fully functional photoreceptors are formed *in vivo* (Bartsch et al., 2008; Klassen et al., 2007; Qiu et al., 2005).

Another stem/progenitor cell type that is often utilized in preservation strategies is neural stem/progenitor cells (NSCs/NPCs). Similar to RSCs/RPCs, NSCs/NPCs can be derived from fetal brain tissue, ESCs, or iPSCs (Sareen et al., 2014; Shelley et al., 2014; Svendsen et al., 1997). NSCs/NPCs are self-renewing, multipotent cells that are able to differentiate into cells of the nervous system. Unlike RSCs/RPCs, NSCs/NPCs do not differentiate into mature retinal cells, and instead may aid in photoreceptor preservation by secreting

neurotrophic factors and phagocytizing photoreceptor outer segment (Cuenca et al., 2013; Gamm et al., 2007; Nishida et al., 2000; Tsai et al., 2015). NSCs/NPCs can be transplanted via subretinal injection and typically do not integrate within the host photoreceptor layer, yet the cells can migrate within the subretinal space following subretinal injection to exert an effect on a larger portion of the retina (Banin et al., 2006; Lu et al., 2015; Meyer et al., 2006; Tsai et al., 2015). Each type of cell has individual benefits as a preservation strategy, but the true test will be in efficacy results following clinical trials in humans.

3.4.2. Animal studies and clinical trials of preservation strategies—Six clinical trials are currently registered for the use of MSCs in treating either AMD or RP; however, only those with published preclinical or preliminary results will be discussed. In the United States, Janssen Research and Development LLC has two clinical trials testing a UC-MSC line, CNTO 2476, for AMD (NCT02659098 and NCT01226628). Preclinical studies of a subretinal transplantation of UC-MSCs into RCS rats were found to prevent vision loss and rescued photoreceptor cells (Lund et al., 2007). To test for safety, the Phase I/IIa study will use the CNTO 2476 cells in subretinal injections by micro catheter (NCT01226628) and the Phase IIb trial will perform a similar study using a subretinal access kit (SRAK-02) (NCT02659098). BM-MSCs are also being used in clinical trials, as studies using BM-MSCs in retinal degenerate rodent models aided in rescuing vision loss (Figure 3B), photoreceptor cell survival (Figure 3C and C'), and can be used as autologous transplants (Arnhold et al., 2007; Lu et al., 2010; Otani et al., 2004). In the United States, a Phase I trial by the University of California, Davis is using autologous bone marrow derived CD34+ cells (NCT01736059). The benefit of using this subset of cells is that CD34+ cells can home to damaged retina, have long-term survival, and may have enhanced progenitor activity (Otani et al., 2004; Park et al., 2012; Sidney et al., 2014). Preliminary results from the intravitreal injection of autologous BM-derived CD34+ cells did not show intraocular inflammation or hyperproliferation in patients with ischemic or degenerative retinal disorders, including AMD, Stargardt macular dystrophy, and RP, suggesting that the treatment is feasible and safe for various retinal disorders (Park et al., 2014). For the remaining clinical trials, no reports have yet been published and there is limited information on the use of MSCs in patients with retinal degeneration.

One of the benefits of using RSCs/RPCs would be the potential for the cells to integrate and mature into photoreceptor cells *in vivo*. At such early stages in clinical trials, only the safety of RSC/RPC administration is being evaluated. A subretinal injection of fetal tissue derived-RPCs into RCS rats had no tumor formation or other adverse effects and had visual function preservation (Luo et al., 2014). In addition, preclinical studies have shown that human RSC/RPC xenografts are able to integrate within the degenerate retina, express photoreceptor-specific proteins, and differentiate into mature retinal cell types (Aftab et al., 2009; Klassen et al., 2007; Qiu et al., 2005; Warfvinge et al., 2005). In the United States, two Phase I/II clinical trials for RP are underway. jCyte Inc. is sponsoring a Phase I/II trial using intravitreal injections of RPCs (jCells) at differing concentrations (5×10^5 and 1×10^6) (NCT02320812). No safety concerns have been reported and the secondary outcome is ocular function. One published article from initial studies of these cells suggests that the standard immunosuppression regimen in RCS rats post-surgery causes differences in OKR

and ERG performance; however, these tests were performed on untreated animals and no results from transplantation with RPCs have yet been reported (Cooper et al., 2016). The second clinical trial is sponsored by ReNeuron. To evaluate safety and tolerability, fifteen patients received a single subretinal injection of RPCs and data are expected during the second half of 2016 (NCT02464436). Though the goal of RSC/RPC trials is safety, secondary outcomes of efficacy will determine photoreceptor and visual function preservation with the use of retinal lineage-specific cells.

At this time, no clinical trial is ongoing for the use of NSCs/NPCs in retinal degenerative diseases, but results from multiple preclinical studies have shown promising results. StemCells, Inc. sponsored and completed a trial using human fetal-derived NSCs (HuCNS-SC) for evaluating safety in AMD patients (NCT01632527). A long-term follow-up study over four years was recently terminated due to business reasons and not due to safety concerns (NCT02137915). Preclinical studies using HuCNS-SC showed photoreceptor and visual function preservation in RCS rats with limited proliferation, no tumor-like formation, and phagocytic capacity *in vivo* (Cuenca et al., 2013; McGill et al., 2012). A similar fetal-derived NPC cell line (hNPCs) was shown to have similar beneficial effects in RCS rats. At age P100, RCS rats treated with hNPCs exhibited near-normal visual acuity and hNPCs survived in the subretinal space up to seven months of age with concomitant photoreceptor preservation (Gamm et al., 2007; Wang et al., 2008). The hNPCs were also tested in rhesus macaques with no inflammation or rejection, and the cells survived within the subretinal space to the end of study at 39 days following injection (Francis et al., 2009). To bypass ethical concerns of fetal tissue derivation, NSCs/NPCs can also be derived from ESCs or iPSCs. Studies using iPSC-derived NPCs (iNPCs) have shown that a subretinal injection is able to preserve visual function (Figure 3D) and photoreceptor cells (Figure 3E and E') (Tsai et al., 2015). In addition, the photoreceptor rescue correlated specifically with presence of the NSCs or iNPCs within the subretinal space and performed phagocytosis of photoreceptor outer segments *in vivo*, suggesting that the rescue effect is not solely due to neurotrophic benefits (Cuenca et al., 2013; Tsai et al., 2015). The many benefits and studies of NSCs/NPCs will ultimately lead to future clinical trials for patients with retinal degenerative diseases.

Another preservation strategy is using RPE as purely supportive, secretory cells. In the United States, Neurotech Pharmaceuticals has two Phase II clinical trials testing the use of an encapsulated RPE cell line. CNTF secreting RPE cells are embedded as an intraocular implant (NT-501) in AMD patients (NCT00447954) or RP and Usher Syndrome patients (NCT01530659). In these instances, the RPE cells do not integrate and attach to the Bruch's membrane and instead act as factories of neurotrophic factors for preservation. Results from the CNTF secreting RPE cells trials determined that the implants were safe, and that CNTF was consistently produced by the implants over a 2-year period (Kauper et al., 2012; Zhang et al. 2011). The benefit of preservation strategies is the wealth of cell types for transplantation and study, allowing for multiple options and modalities for treatment

4. Future directions

4.1. Continuing obstacles for cell-based therapies for retinal degeneration

4.1.1. Scientific basis—Common themes arise with the use of either replacement or preservation strategies and the concerns differ from the perspective of the scientist or clinician. From the benchside perspective, the main difficulties are in the cells themselves. The answer may be patient-specific and depend upon the severity of disease, thus certain cells will be meaningful in one disease or situation yet rendered impractical in other circumstances. Regardless of the cell type, imperfect reprogramming or differentiation from ESCs or iPSCs could be an issue. Because there is not a complete, 100% reprogramming efficiency, then cells would need to be grown in culture for an extended period of time to generate enough cells for testing and eventual transplantation. In the clinical study conducted in Japan, iPSC-RPE were found to have mutations, and it is unclear if this was due to the reprogramming process or if these mutations were in cells prior to induction of pluripotency. This would be a continual concern, as reprogramming and derivation processes would be performed on each patient's cells for generation of autologous transplants. Protocols are lab preferential; therefore, these variables should be taken into account if separate labs at different facilities are performing similar tasks of preparation. In addition to karyotypic abnormalities during reprogramming, autologous iPSCs will still carry disease causing mutations. It is unclear if this will cause difficulties in AMD patients, since it is a multifactorial disease with age as one contributing variable. Mutations in endogenous RPE cells led to the disease over decades of the patient's life and would require that the new iPSC-RPE be subjected to the same factors to become diseased cells themselves. Two possibilities are that the cells may survive and function properly for the remainder of the aged patients' lives or quickly become dysfunctional within the degenerative environment. With the evolving use of the CRISPR/Cas9 system for gene editing, future therapeutics may take into account disease-causing mutations, such as those for RP, and choose to correct them before transplantation (Bassuk et al., 2016; Cong et al., 2013; Kime et al., 2016).

A question specific to RPE replacement therapies is transplantation of cells with or without a standardized scaffold. Single cell suspensions, RPE sheets, and scaffold tethered RPE are in clinical trials for AMD. The consenting opinion seems to be that RPE sheets are the best option for transplantation, as RPE cell sheets have enhanced stability and survival, yet there has been little evidence for prolonging photoreceptor survival (Diniz et al., 2013; Kamao et al., 2014). Delivery of an RPE sheet or scaffold close to the macula is an invasive procedure and carries an added risk of compromising remaining macular vision. If the cells are attached to a scaffold, then RPE cells will not need to migrate from the injection site or find availability on the Bruch's membrane; however, synthetic scaffold materials may cause structural differences in RPE cells, physically separate the RPE from the underlying choroid, and cause inflammation (Bhatt et al., 1994; Brant Fernandes et al., 2016; Diniz et al., 2013; Lee et al., 2002; Sorkio et al., 2014; Tezel and Del Priore, 1998). The caveat to single cell RPE suspensions is the distribution, polarity, and attachment to the Bruch's membrane, as non-integrating RPE cells are at risk for ingestion by macrophages (Westenskow et al., 2016). Both ESC- and iPSC-RPE display polarization with regards to structure, function, and secretion of factors, but the long-term maintenance of these factors *in vivo* have not

been tested (Brandl et al., 2014; Hirami et al., 2009; Muniz et al., 2014; Singh et al., 2013; Vugler et al., 2008; Zhu et al., 2011). Attachment to the Bruch's membrane may aid in the polarization process of RPE cells, yet the ability of RPE cells to adhere may be at risk. The Bruch's membrane undergoes degenerative changes with age and AMD, and ESC-RPE may have issues with attaching and functioning properly (Sugino et al., 2011, 2014). Though RPE delivery has its limitations, the type of graft may be determined on a patient-to-patient basis contingent upon the integrity of the Bruch's membrane.

4.1.2. Clinical aspects

4.1.2.1. Cell survival, immunogenicity, and multiple dosages: Many factors contribute to cell survival following transplantation. Current cell delivery system needs to be improved and standardized. Cells are typically prepared from frozen stocks and can undergo cell death due to the freezing and thawing process, and differences in cryopreservation techniques may affect initial post-thaw viability (Milosevic et al., 2005). To ensure the safety and standardization of cell transplantation, the FDA has set an acceptable requirement for cell therapeutic products at a minimum of 70% recovery (Mendicino et al., 2014). Once prepared, cells may undergo mechanical shearing during ejection through a syringe, needle, or cannula. Differing cell sizes and types, ranges in needle sizes, expertise of the surgeon, and ejection rates introduces more variability on the technique for transplantation (Amer et al., 2015, 2016; Ballios et al., 2015; Mamidi et al., 2012). Ejection rate has an effect on cell viability and health post-transplantation, and cell delivery may require pre-treatment or co-injectable materials, such as injectable hydrogels, to aid in cell survival (Aguado et al., 2012; Amer et al., 2016; Ballios et al., 2015). Once cells are transplanted, one of the main issues from both a biological and therapeutic aspect is the possibility of adverse immune responses to injected cells. While transplanted cell survival rates are generally low, certain measures can guard against loss of cells, such as the use of immunosuppressive agents and maintaining the blood retinal barrier during surgery (Del Priore et al., 2003; Lu et al., 2010; Xian and Huang, 2015). Resident immune cells of the retina, including microglia, can become activated during degeneration and in this heightened immune state may affect the viability of the grafted cells (Barker and Widner, 2004; Karlstetter and Langmann, 2014). Conversely, the grafted cells themselves may be able to combat this by secreting factors to modulate the immune response (Baraniak and McDevitt, 2010; Jones MK et al., 2016). A majority of the clinical trials have detected minimal immune-related responses due to the cells themselves, and re-dosing studies in animals have shown that there is no adverse response to second injections while on immunosuppression (Lu et al., 2015). In the event that there is rejection, the possibility of surgically removing the graft would be difficult. In the case of RPE cells affixed on a scaffold, the cells may not migrate and the entire transplant could be extracted and would be an invasive procedure, whereas locating and selecting suspended single cells from RPE replacement or any preservation therapy would be nearly impossible. *In vivo* imaging systems, such as two-photon imaging, are able to detect differences in retinal thickness, light stimulation, and single cells in animal models, but detecting and then extracting these cells would not be feasible in humans, and the patient would be subjected to any lingering adverse effects of the cells (Bar-Noam et al., 2016; Maeda et al., 2014; Sharma et al., 2016).

In current clinical trials, a single injection is performed with the main focus on safety. To achieve maximal preservation of vision, multiple injection sites may be necessary. In addition to multiple sites, there may also be a need for repeat injections over time. If there is not enough cell survival and engraftment, or if the cells die over the life of the patient, then it may be possible and necessary to inject more cells. Although RPE or supportive cells can be cultured and expanded *in vitro*, the cells have not been shown to be proliferative *in vivo* (Kanemura et al., 2014; Lu et al., 2015; Stanzel et al., 2014). While this suggests no tumorigenesis, it also indicates that cells cannot replenish themselves. NPCs are well-tolerated and survive within the subretinal space for extended periods of time, and re-dosing studies have not shown immune-related responses (Lu et al., 2015); however, the feasibility of re-dosing has not been tested in clinical studies.

4.1.2.2. Interventional timing: There may be a point of no return, at which no intervention would rescue/restore vision. In the case of RPE cell suspension replacement therapy, endogenous dysfunctional, surviving RPE cells would cause more problems because they are attached to the Bruch's membrane and would not allow for engraftment of new RPE cells. The time point at which host RPE cells are absent yet photoreceptors are still present would be an ideal situation for RPE replacement therapy. Since there is also variation in the presentation of disease, further anatomical and integrity studies (e.g. OCT analysis) may be needed to gauge the extent of photoreceptor or RPE cell survival. For RPE replacement strategies, it may be possible to increase the range of patients to include those who have lost a number of photoreceptor cells. RPE cells could be injected with photoreceptor cells, either as single cell suspensions or 3D pieces of retinal tissue. It is estimated that 60,000 RPE cells would be necessary to cover the macula for preservation of central vision (Bharti et al., 2011). Neonatal retinal sheets consisting of neural retina and RPE are able to survive and differentiate after subretinal transplantation and make connections to the host retina with slight visual improvement (Ghosh et al., 2004; Humayun et al., 2000; Radtke et al., 2002; Seiler et al., 2008). Patients that receive an implant containing neural retinal sheets with RPE had no rejection with varying visual acuity outcomes (Radtke et al., 2008). Similar grafted tissue could be generated using either ESC- or iPSC-derived RPE and photoreceptor layers to benefit patients with severe degeneration, if the grafts are able to integrate and/or communicate with the host retina. For photoreceptor preservation strategies, early interventation leads to better preservation of vison. Though not discussed in this review, photoreceptor replacement therapy is also being used as a treatment for progressive retinal degenerative disorders (please refer to reviews by Jayakody et al., 2015; Pearson, 2014; Ramsden et al., 2014; Reh, 2016).

4.1.2.3. Site of graft placement: The location of the transplant is also of importance. Since the macula is affected in AMD, transplanted RPE cells should be close to the macula or areas of geographic atrophy, but transplantation causes a retinal detachment and more damage, which has a high risk of compromising macular vision. Also, if there are multiple sites of geographic atrophy, then there might need to be multiple implants or sites of injection. In the case of RP, the peripheral retina is initially affected and multiple sites of injection may also be needed to encompass a satisfactory area of preservation for macular vision. While RPE cells have a limited migratory ability, some cell types, such as NPCs, are

able to migrate away from the injection site, but it is unknown how far the cells will travel in diseased eye and if the benefit is similar to animal studies (Gamm et al., 2007; McGill et al., 2012; Tsai et al., 2015). The fovea constitutes an area of 1.8 mm^2 and NPCs were found to migrate over a distance of 5 mm, suggesting that the cells could be transplanted in an extrafoveal location to avoid compromising central vision (McGill et al., 2012; Tsai et al., 2015). Some presumptions can be extrapolated from animal studies, but the true test will be the performance in humans.

4.1.2.4. Delivery system: Currently, there is no standardized guidance for the injection volume, cell concentration and speed in clinical trials. It is estimated that 60,000 RPE cells would be needed to cover the macula for preservation of central vision (Bharti et al., 2011). Most preclinical studies have been conducted in rodent models, which have a small eye size thus limiting the volume that can be injected. A simple scale-up based on retinal areas of animal models to humans may not be rational, since the main purpose is to protect the macula and not the whole eye. Current clinical trials have injected 100–150 uL of cell suspensions, yet the cell concentration (cells/uL) were much lower than those used in animal studies. The behavior and function of cells in low densities has not been elucidated and it is unclear the exact amount or range of cell numbers needed for efficient transplantation.

4.1.2.5. Clinical validation: Most animal models of retinal degeneration have a relatively fast rate of degeneration, and the effect from treatment can be determined within a short period of time, yet the slow progression in humans is difficult for short-term evaluations of efficacy. Although ERG can reveal the difference between treated and control animals, it is not a sensitive measurement for a localized effect induced by a single subretinal injection. Advances in *in vivo* imaging systems, such as adaptive optics scanning laser ophthalmoscopy (AOSLO) and spectral domain optical coherence tomography (SD-OCT), may allow for the monitoring of retinal lamination, cellular changes, progression of disease, and response to treatment.

The most sensitive method to detect the localized effect is to record luminance threshold responses (LTR) in the superior colliculus to small light spots of varying position in the visual field, the multi-unit response threshold can detect the local rescue effect in animals. This method is based on the topographic projection from the retina to the superior colliculus. The use of LTR in humans is not possible, but Once visual function is detected, the results from the studies may be open to interpretation and the outcomes may vary depending on goal of study or patient variation (Schwartz et al., 2015a; Sunness, 2015; Zhang et al., 2015). The rodent's lifespan is approximately 2 years, yet the duration for most transplantation studies is limited to 5 to 8 months due to the side effects from immunosuppression in xenograft conditions. Animal studies have shown grafted RPE cells have long-term survival, yet there has been no correlation detected between graft survival and photoreceptor rescue, suggesting that grafted RPE cells do not replace endogenous RPE cells or the effect is not long lasting (Lu et al., 2009; Westenskow et al., 2016). For AMD patients, the grafted RPE cells will need to survive and function potentially for decades, and the attachment, functionality, and survival of transplanted RPE cells onto an aged Bruch's membrane and in the degenerative environment will be examined in current clinical trials.

4.1.2.6. Financial burden: Lastly, the cost of conducting preclinical and clinical studies is large, and once these therapies are brought to clinic then the burden of payment can fall to many individuals (Shah and Williams, 2016). The cost of development of a new drug is estimated at 2.6 billion US dollars and is increasing (DiMasi et al. 2016). Many drugs or therapeutics do not even reach the marketplace as a number of factors lead to discontinuation of drug development, including toxicity and lack of efficacy (Laustriat et al., 2010). Companies will need to profit from the therapy, and this charge will likely be aimed at insurance companies or patients. The justification of cell therapies has not reached the mainstream market, so insurance companies may not be willing to cover the cost of investigational or non-standard treatments. The hope that cell therapies are safe and efficacious will justify some of the cost, but the benefit to patients should be the ultimate goal for scientists and clinicians alike.

4.2. Enhancing efficacy

Clinical trials for cell based therapies are in its infancy so the extent of efficacy is unknown in humans. The future of cell therapies relies on both the beginning tests of safety, with goals set for learning how to improve efficacy. To do this, more mechanistic studies of stem cell therapies should be performed. With RPE replacement therapies, the intended mechanism is mainly understood, and results from the current clinical trials will either confirm or disprove this hypothesis. To enhance the performance of the cells, the grafted RPE cells could be modified for greater potency if induced to secrete more RPE-specific or other neurotrophic factors or have better engraftment. Improving the host microenvironment, such as promoting RPE cell engraftment, has been effective in animal studies (Afshari and Fawcett, 2009). The confounding questions of mechanism mainly surround the use of preservation strategies. For NPCs, studies have shown that they are able to phagocytose shed outer segments and secrete some neurotrophic factors, but the direct cause of photoreceptor preservation is unknown (Cuenca et al., 2013; Tsai et al., 2015). In the case of MSCs, it is thought that they able to influence the immune response, but how this affects vision is unknown. Other retinal cells, such as retinal astrocytes and Müller glia, also play roles in the homeostasis and functioning of retinal neurons, and there may be indirect effects on other retinal cells. Müller glial cells participate in metabolic support of retinal neurons by secreting neurotrophic factors necessary for photoreceptor survival (Harada et al., 2003; Shen et al., 2012; Tsacopoulos and Magistretti, 1996). Astrocyte activation and reactive gliosis occurs in neurodegenerative processes, and a characteristic feature is the upregulation of certain intermediate filament proteins, including glial fibrillary acidic protein (GFAP), vimentin, and nestin (Anderson et al., 2008; Luna et al., 2010). While certain neuroprotective factors may be beneficial, chronic gliosis may also accelerate neurodegeneration (Coorey et al., 2012).

Combination therapies with multimodal delivery systems may be more beneficial than one cell type. Multiple cell types or deliveries, such as both subretinal injection of NPCs and systemic delivery of MSCs, may be needed for an added effect. Each has specific tasks that they are able to perform within the retina, but may work synergistically when injected simultaneously or in tandem. Systemic delivery of MSCs may be able to offer immunomodulatory effects, which could allow for better engraftment of cells, such as RPE or NPCs (Bakondi et al., 2016; Maitra et al., 2004; Ren et al., 2008). Cells could also be pre-

conditioned, as cells grown with different culture conditions have different gene expression profiles, or induced to overexpress growth factors for greater efficacy *in vivo* and RPE attachment to Bruch's membrane (Afshari and Fawcett 2009; Gamm et al., 2007; Sugino et al. 2014). Changing the environment of cells prior to cell injection could allow the cells to be better prepared for engraftment or survival. In addition to preparing the cells for injection, there may be benefits to priming the host tissue before transplantation. The host tissue response is different when cells are injected versus sham surgery, suggesting that the host tissue could also be primed prior to transplantation for better reception of cell transplantation (Jones et al., 2016). At this time, the main focus on cell-based therapies is on safety in humans, yet the future of these therapies rests on the potential benefits with the next task of efficacy.

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Abbreviations

AMD	age-related macular degeneration
AOSLO	adaptive optics scanning laser ophthalmoscopy
BDNF	brain-derived neurotrophic factor
bFGF	basic fibroblast growth factor
BM-MSC	bone marrow derived-mesenchymal stem cell
CFH	complement factor H
CNTF	ciliary neurotrophic factor
ERG	electroretinography
ESC	embryonic stem cell
GDNF	glial cell line-derived neurotrophic factor
INL	inner nuclear layer
iNPC	induced pluripotent stem cell-derived neural progenitor cell
iPSC	induced pluripotent stem cell
LCA	Leber congenital amaurosis
LTR	luminance threshold response
MHC	major histocompatibility complex
MSC	mesenchymal stem cell

NPC	neural progenitor cell
NSC	neural stem cell
ONL	outer nuclear layer
PEDF	pigment epithelium-derived factor
PGF	placental growth factor
RCS	Royal College of Surgeons
RDDs	retinal degenerative diseases
RGC	retinal ganglion cell
RHO	rhodopsin
RP	retinitis pigmentosa
RPE	retinal pigment epithelium
RPC	retinal progenitor cell
RSC	retinal stem cell
SD-OCT	spectral domain optical coherence tomography
UC-MSC	umbilical cord-derived mesenchymal stem cell
VEGF	vascular epithelial growth factor

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Article Highlights

- Cell-based therapies offer new modes of treatment for retinal degeneration.
- Replacement strategies for AMD aim to transplant new retinal pigment epithelium.
- Preservation cell treatment aids in supporting remaining photoreceptors and vision.
- Many hurdles remain for cell-based clinical trials of retinal degenerative diseases.

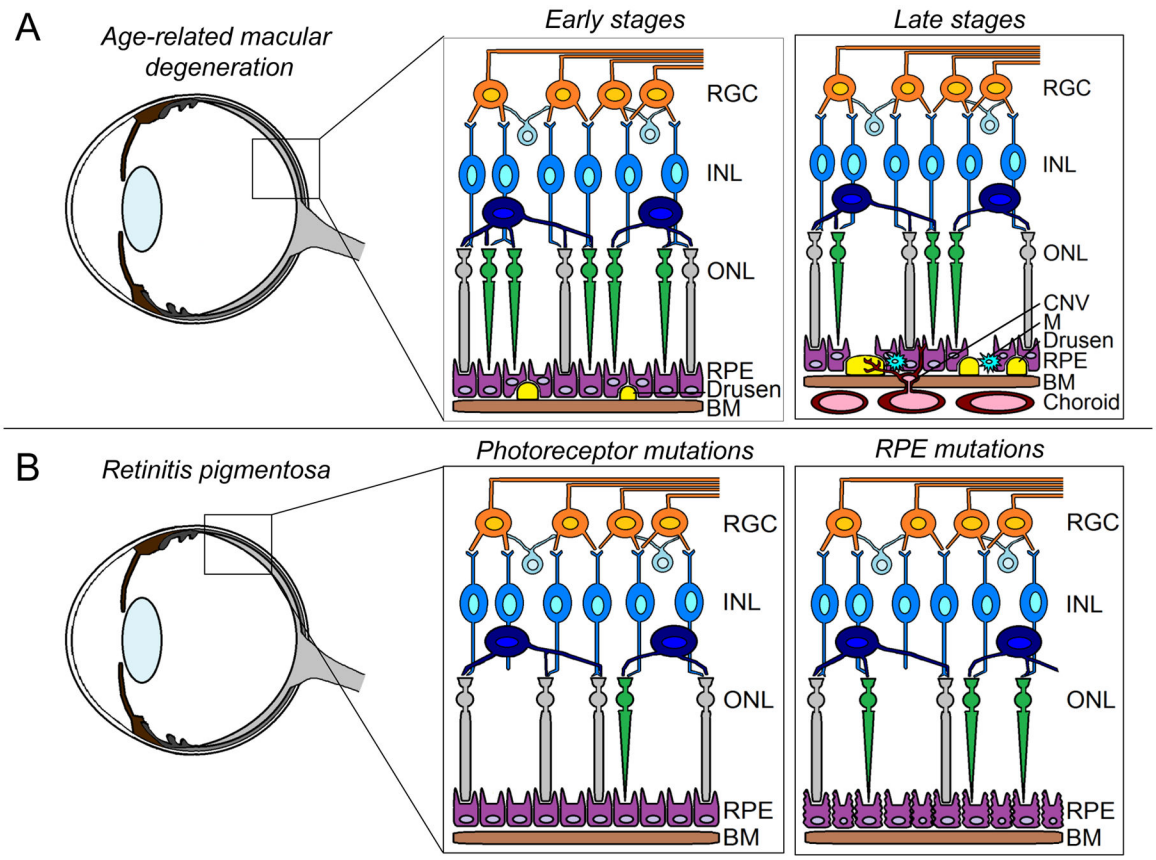

Figure 1.

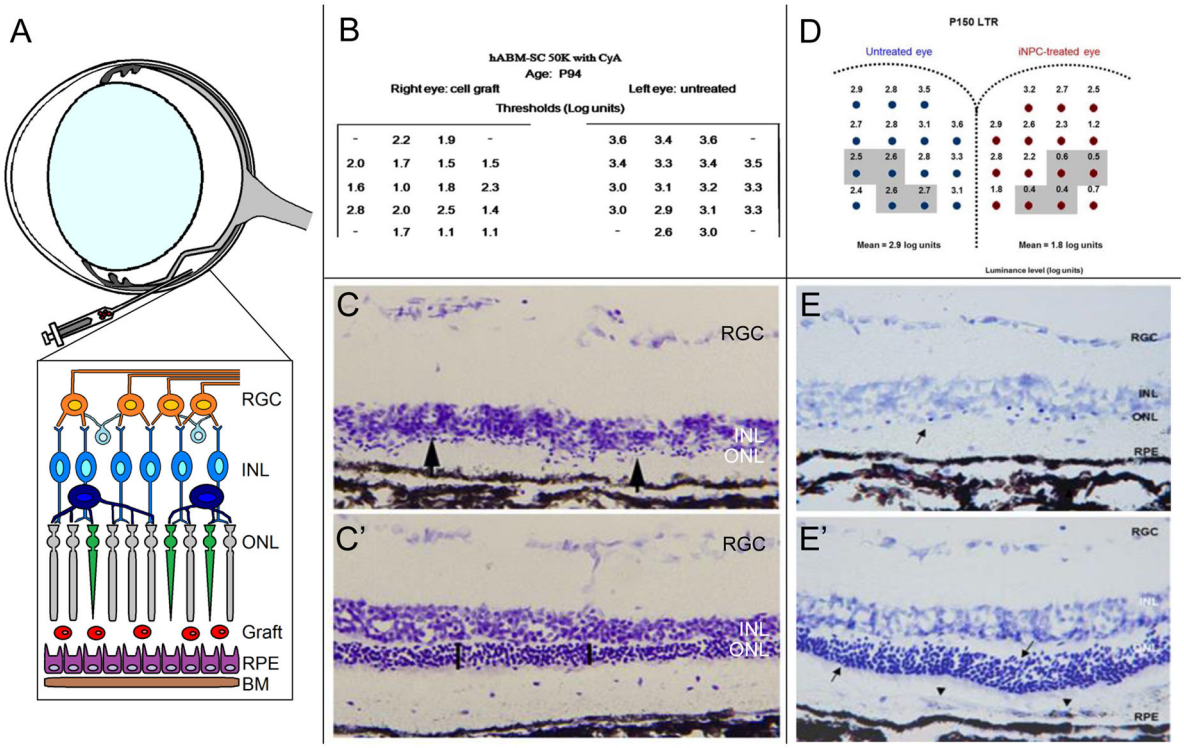

Figure 2.

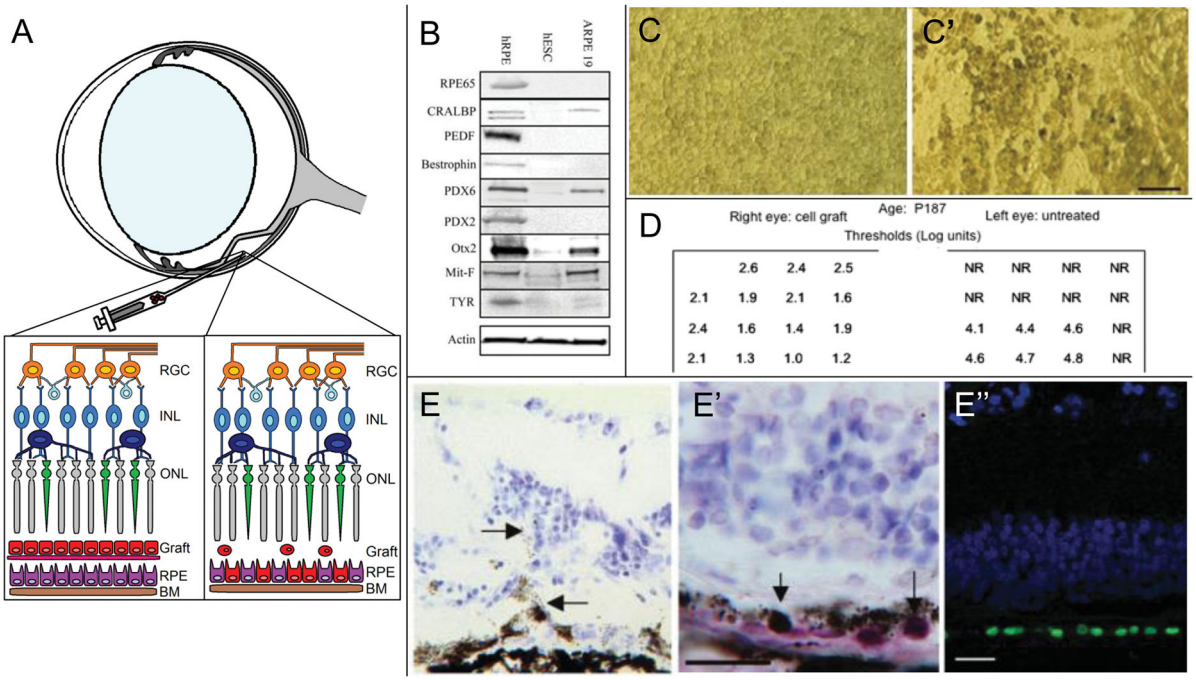

Figure 3.

Table

Status of registered clinical trials using cell-based therapies for AMD and RP.

Sponsor	Disease	Status	Evaluation	Treatment/Intervention	Countries	Updated	ID
Astellas Institute for Regenerative Medicine	Dry AMD	Phase I/II – Completed	Safety and efficacy	Subretinal transplantation of human embryonic stem cell derived retinal pigment epithelium (MA09-hRPE) cells	USA (California, Florida, Massachusetts, Pennsylvania)	17-Aug-16	NCT01344993
Astellas Institute for Regenerative Medicine	Advanced dry AMD	Ongoing, not recruiting	Safety and efficacy	Subretinal injection of human embryonic stem cell derived retinal pigment epithelium cells (MA09-hRPE)	USA (California, Florida, Massachusetts, Pennsylvania)	10-Jun-16	NCT02463344
Astellas Institute for Regenerative Medicine	Dry AMD	Phase II - Recruitment suspended, lack of investigational product availability due to planned changes to the cell line	Safety	Subretinal transplantation of MA09-hRPE cells with low-dose systemic immunosuppressive therapy as rejection prophylaxis	USA (Pennsylvania)	10-Jun-16	NCT02563782
Cell Cure Neurosciences Ltd.	Advanced dry AMD	Phase I/II - Recruiting	Safety and efficacy	Subretinal transplantation of human embryonic stem cell derived retinal pigmented epithelial (OpRegen) cells	Israel	5-Oct-16	NCT02286089
CHABiotech CO., Ltd	Dry AMD	Phase I/IIa - Unknown	Safety and efficacy	Subretinal transplantation of human embryonic stem cell derived retinal pigmented epithelial (MA09-hRPE) cells	Republic of Korea	22-Oct-12	NCT01674829
Chinese Academy of Sciences	AMD	Phase 0 - Recruiting	Safety and efficacy	Subretinal transplantation of clinical human embryonic stem cell derived retinal pigment epitheliums	China	26-Apr-16	NCT02755428
Moorfields Eye Hospital NHS Foundation Trust	AMD	Not yet open for recruitment	Feasibility	Production of induced pluripotent stem cell derived retinal pigment epithelial cells for human transplantation	UK	3-Jun-15	NCT02464956
Pfizer, University College, London	Wet AMD	Phase I - Ongoing, not recruiting	Safety and feasibility	Implantation of Pf-05206388 (monolayer of human embryonic stem cell derived retinal pigment epithelial cells on a polyester membrane)	UK	5-Dec-16	NCT01691261
Regenerative Patch Technologies	Dry AMD	Phase I/IIa - Recruiting	Safety and efficacy	Subretinal implantation of CPCB-RPE1 (human embryonic stem cell-derived retinal pigment epithelial cells seeded on a polymeric substrate)	USA (California)	26-Jun-16	NCT02590692
Southwest Hospital, China	Macular degeneration diseases (AMD & Stargardt's macular dystrophy)	Phase I - Recruiting	Safety and efficacy	Subretinal transplantation of human embryonic stem cell derived retinal pigment epithelium (hESC-RPE)	China	20-Apr-16	NCT02749734
University of California, Los Angeles and Ocata Therapeutics	Myopic macular degeneration	Phase I/II – Withdrawn prior to enrollment, study under revision	Safety	Subretinal transplantation of human embryonic stem cell derived retinal pigmented epithelial (MA09-hRPE) cells	USA (California)	14-Jul-16	NCT02122159
Al-Azhar University	Geographic atrophy secondary to AMD	Phase I/II - Unknown	Safety and efficacy	Intravitreal transplantation of adult bone marrow stem cells	Egypt	20-Dec-13	NCT02016508
Janssen Research and Development LLC	Geographic atrophy secondary to AMD	Phase IIb - Recruiting	Safety	Subretinal injection of CNTO 2476 (human umbilical tissue derived)	USA (California, Illinois, Kentucky, Massachusetts, Michigan, Ohio, Pennsylvania, Texas)	26-Oct-16	NCT02659098

Sponsor	Disease	Status	Evaluation	Treatment/Intervention	Countries	Updated	ID
Janssen Research and Development LLC	AMD	Phase I/IIa - Ongoing, not recruiting	Safety	Subretinal administration of CNTO 2476 (human umbilical tissue derived)	USA (California, Pennsylvania)	19-Dec-16	NCT01226628
Red de Terapia Celular	RP	Phase I - Recruiting	Safety	Intravitreal injection of autologous bone marrow stem cells and subconjunctival injection of saline	Spain	30-Sep-15	NCT02280135
University of California, Davis	Retinopathy (Including AMD & RP)	Phase I - Invitation only	Safety and feasibility	Intravitreal bone-marrow CD34+ bone marrow stem cells	USA (California)	7-Jan-16	NCT01736059
University of Sao Paolo	AMD	Phase I/II - Unknown	Safety	Intravitreal injection of autologous bone marrow stem cells	Brazil	3-Dec-14	NCT01518127
jCyte, Inc	RP	Phase I/II – Ongoing, not recruiting	Safety - dosage	Intravitreal injection of human retinal progenitor cells (jCell)	USA (California)	15-Dec-16	NCT02320812
ReNeuron Limited	RP	Phase I/IIa - Recruiting	Safety - dose escalation	Subretinally transplanted human retinal progenitor cells (hRPC) open-label, first-in-human	USA (Massachusetts)	16-Dec-16	NCT02464436
StemCells, Inc.	Geographic atrophy of AMD	Terminated - Unrelated to safety concerns	Safety and efficacy	Subretinal transplantation of human central nervous system cell stem cells (HuCNS-SC)	USA (Texas)	31-May-16	NCT02137915
StemCells, Inc.	AMD	Phase I/II - Completed	Safety and efficacy	Subretinal transplantation of HuCNS-SC (human central nervous system stem cells)	USA (California, New York, Texas)	10-Sep-15	NCT01632527
Neurotech Pharmaceuticals	RP, Usher Syndrome Type 2 or 3	Phase II – Ongoing, not recruiting	Photoreceptor structure, cone spacing, and density	Encapsulated Human NTC-501 cell implants releasing ciliary neurotrophic factor (CNTF)	USA (California)	26-Oct-16	NCT01530659
Neurotech Pharmaceuticals	Dry AMD	Phase II - Completed	Safety and efficacy	Implantation of NT-501 (capsule of human retinal pigment epithelial cells secreting CNTF)	USA (California, Florida, Massachusetts, Michigan, Texas, Utah)	15-Nov-16	NCT00447954