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White Paper

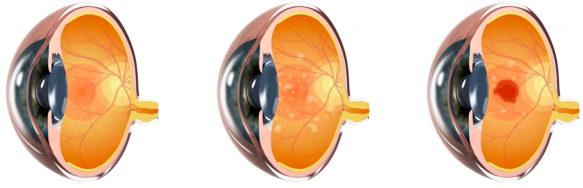
Stem Cell Therapy for Macular Degeneration: Current Insights and Future Prospects

Age-related macular degeneration (AMD) is a highly prevalent eye disorder with a typical onset in people aged 50-60 years. The condition affects specialized retinal pigment epithelium (RPE) cells, which cover the Bruch's membrane at the back of the eye, and are central to the health and function of light-detecting photoreceptor cells in the retina. AMD is characterized by dysfunction or death of RPE cells in the macula region, which in turn prompts a loss of photoreceptor cells leading to permanent loss of central vision.

AMD has been shown to be widely heterogeneous, with a host of genetic, epigenetic, age-related and lifestyle influences. It is the leading cause of blindness in developed countries, with the number of people with AMD globally predicted to increase from 196 million in 2020, to 288 million by 2040 [1]. The disease is categorized into early, intermediate, and late stages. While early and intermediate AMD stages bring little to no visual symptoms, loss of central vision is often severe and irreversible with late stage AMD. The high prevalence of AMD creates major consequences for individuals and society alike, as growing numbers of AMD patients experience decreased quality of life and independence.

Traditional treatment options for AMD are limited in their efficacy and application, and access to treatment is dependent upon the manifestation of the disease. Neovascular (wet) AMD, defined by abnormal neovascularization in the macular region, is the more acute and severe form of AMD, and has therapeutic options of anti-VEGF medication (antiangiogenics), or photodynamic therapy (PDT). Atrophic (dry) AMD, characterized by the build-up of drusen deposits in the macular region, is the more chronic and gradual form of the disease. Although the significantly more common form, dry AMD has had no traditional therapeutic options to speak of [2]. As such, there is an urgent demand for novel therapeutics, especially in the case of dry AMD.

FIGURE 1. Retina changes in AMD



HEALTHY EYE | DRY AMD | WET AMD

In recent years, the emergence of cell therapy technologies have piqued great interest from researchers and clinicians seeking to develop targeted AMD cell therapies. Through cell therapy, functional RPE cells can be transplanted into a patient's eye to prevent the loss of photoreceptor cells and thus halt the progressive loss of vision. In this article, we will investigate the current landscape of AMD cell therapy, and posit future prospects and challenges for this exciting emerging technology.

Cell Therapy for AMD

The emergence of cell therapy technologies has transformed regenerative medicine into one of the fastest growing research and development areas in life sciences today. By transplanting functional cells into the body, damaged or dysfunctional cells and tissue can be replaced to generate stunning therapeutic results. The eye in particular represents a very favorable target organ for cell therapies due to its ease of accessibility and immuno-privileged nature, meaning that immune and inflammatory responses are limited, reducing the likelihood of graft rejection.

The discovery of induced pluripotent stem cells (iPSCs) in 2007, and subsequent Nobel Prize award in 2012 [3], inspired a surge of research seeking to develop iPSC-

based cell therapies to combat AMD. The elegant technique of iPSC therapy takes a patient's adult somatic cells, usually from skin or blood, and reprograms them into an undifferentiated embryonic-like pluripotent state. These cells can then be prompted, with gene editing and/or growth factors, to differentiate into any type of human cell required for therapeutic purposes.

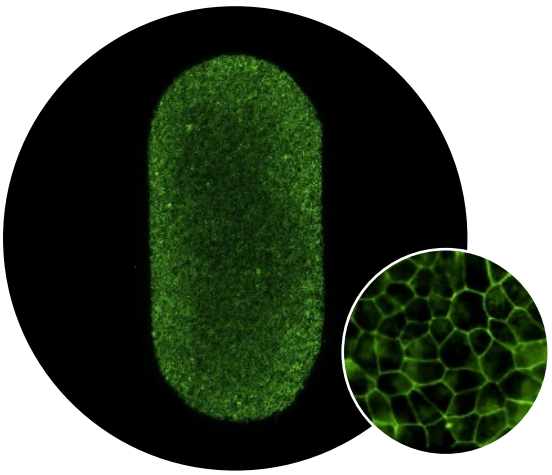
RPE Cell Transplantation

On the back of the success of iPSC technology, a novel stem-cell therapy based upon iPSC-derived RPE cell transplantation was conceptualized as a promising new treatment for AMD and other retinal diseases. RPE cell transplantation aims to halt or reverse AMD-related vision loss by replacing dead or dysfunctional RPE cells, in turn preventing the death of neighboring photoreceptor cells. RPE replacement is considered one of the most promising applications of stem cell therapy within the field of regenerative medicine [4], and through various iterations, has shown promise in early phase clinical trials.

As with any cell therapy, one of the major challenges posed by RPE transplantation is the delivery of the therapeutic cells to the target region. While the eye represents an accessible organ, different approaches have been trialed to optimize the delivery and integration of RPE cells. Subretinal delivery can be achieved by injecting RPE cells in suspension, but while this method has shown partial success in trials, administering loose cells is a somewhat inefficient technique. Individual cells are more likely to be under stress while in suspension, reducing the chance of efficient self-integration and seeding into the target tissue.

To overcome this, RPE cells can be cultured into a monolayer *ex vivo* in order to mimic the naturally occurring structure. This organoid-type approach ensures that the therapeutic cells are maintained with correct orientation by growing them on a matrix acting as a scaffold. While this method can provide a greater level of treatment efficacy, there is a trade-off to be made in that a significantly more complex surgical procedure is required to inset the patch, and comes with an increased chance of adverse events such as retinal tears or detachments [5].

FIGURE 2.
Example of an RPE patch for AMD cell therapy



RPE Cell Therapy Trial Findings

Since the dry, atrophic form of AMD is more common, and lacks traditional treatment options, many of the clinical trials have been aimed at patients with this from of the disease. At present, several phase I and phase II trials have been conducted, and these have for the most part focused upon safety, rather than effectiveness of treatment, although each trial has attempted to assess the benefit of transplanted RPE cells.

The source of cells in published trials has varied between human embryonic stem cells, induced pluripotent stem cells, and human umbilical tissue-derived cells, while various immunosuppression regimens, surgical approaches, and outcome measures have also been implemented. According to a recent review of early phase studies [6], cell-based therapies in dry AMD (70 patients, 5 trials), wet AMD (12 patients, 4 trials), and Stargardt's macular dystrophy (23 patients, 3 trials) all demonstrated therapeutic safety, albeit most trials also involved immunosuppressive therapy to reduce graft rejection.

While most trials demonstrated survival of functioning RPE cells and visual improvement in some patients, evidence of significant efficacy has not been reported. This is likely due to a combination of factors including a lack of efficacy endpoints, which may not have been defined for a safety-focused trial. Significantly though, one of the major challenges noted by nearly every trial was generating enough RPE therapeutic cells at clinical GMP (cGMP) grade to supply patients with a meaningful therapeutic dose.

The Obstacle of Supply

In order for RPE therapy for AMD to advance further, medium-to-large scale trials will be necessary, and for this, and subsequent therapy roll-outs to become a reality, an efficient manufacturing protocol that can produce pure populations of RPE cells at relevant scale is sorely needed.

Current differentiation protocols generate iPSC-derived RPE cells by spontaneous or directed differentiation approaches. Spontaneous differentiation is labor intensive and highly inefficient, with variable success across different iPSC cell lines. On the other hand, directed differentiation protocols produce substantially greater yields of RPE cells. However, cells differentiated in this way are usually incompatible with cell therapy due to the use of animal-derived products in their production. Any animal-derived product can carry traces of contaminants or pathogens, and bring myriad risks to the patient including infection and immunogenicity.

The pursuit of an efficient GMP compliant protocol to produce differentiated cells therefore requires a full range of animal-free/xeno-free products including iPSC lines, small molecule inducers to direct differentiation, and GMP compatible media and surfaces for cell growth. Large-scale production will also require protocols which allow scale-up of cell production to meet clinical needs beyond clinical trials. For such a prominent condition as AMD, this is especially important, as the demand for therapeutics is extraordinary.

The production of cells at clinical scale will require vigorous, efficient animal-free differentiation protocols capable of producing appropriate numbers of mature therapeutic cells in a reasonable time frame.

Advancing AMD Cell Therapy

As we have discussed, one of the primary barriers to initiating larger-scale trials of RPE cell therapy is the challenge of producing enough therapeutic cells at clinical grade. While this is a source of frustration for researchers and AMD patients, there is hope that the production stalemate can be breached, and that GMP compliant protocols can be improved upon.

One of the first steps toward overcoming production limitations is to increase the availability of animal-free/xeno-free iPS cell lines, media and growth factors for cell culture and differentiation. In a cGMP setting, animal-free products are essential to eliminate the risk of patient infection. Bio-Techne aims to offer a full range of animal-free cell culture products and GMP proteins for clinical manufacturing. The GMP proteins, which include GMP cytokines and growth factors for differentiation have been manufactured to stringent animal-free protocols and regulatory requirements with necessary certifications, ready for use in the clinic.

Another way to help boost success of cell therapies like RPE replacement for AMD at the clinical trial phase, is to conduct preclinical testing with animal-free products such as animal-free proteins early in the development process. Optimizing your research with high quality products early on can help to bring success in your journey to the clinic.

Conclusion

iPSC-based cell therapy appears to be one of the most promising therapeutics to target AMD, and while phase I and II trials have garnered some success, there are significant hurdles to overcome to meet the demands of production and scale-up. If the use of animal-free GMP-compliant culture, media and growth factors could be more widely adopted, the time to clinic for these emerging cell therapies may be reduced significantly. In any case, this exciting technology offers hope to the millions of AMD sufferers around the globe whose vision loss is unresponsive to traditional therapeutics.

Consult the team at Bio-Techne for switching your cell culture products to serum-free, animal-free alternatives tailored to your specific cell types and applications.

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