Special Issue

Stemming the Tide of Age-Related Macular Degeneration: New Therapies for Old Retinas

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Age-related macular degeneration (AMD) is a common, blinding condition that can have a devastating effect on the individuals affected. The loss of central vision, so important for reading, the recognition of faces, and performing many daily tasks, essentially cuts the sufferer off from the world around. There are an estimated 1.75 million cases of late AMD in the United States and half a million in the United Kingdom, all in the over-50 age group.[1] In these cases the macular area of the central retina has lost function either by atrophy in "dry" AMD or by the growth of new blood vessels, which leads to scarring, in the less common "wet" AMD. While there has been great progress in the treatment of wet AMD with development of antivascular endothelial growth factor drugs (anti-VEGF), these treatments are not curative and keep the disease suppressed only with regular intraocular injections.[2] Furthermore, this therapy is expensive, not only in terms of the drug cost but also in clinic time and the human resources necessary for its delivery. Unfortunately, there are no treatments for dry AMD, which accounts for 90% of the disease burden. Thus, AMD represents a major and largely unmet clinical need in an aging population.

The etiology of AMD is multifactorial, like many other age-related diseases. Among the key contributors to the disease process are the loss of the retinal pigment epithelium (RPE) cells and changes in their basement membrane, Bruch's membrane. The RPE is a continuous cellular monolayer lying between the light-sensitive photoreceptors and the choroid, the blood supply of the retina. The photoreceptor cells are responsible for the transformation of light into electrical energy. This process demands significant levels of energy, which in turn creates many free radicals. A lifetime of exposure to these free radicals in the potentially toxic environment of focused light contributes to the degeneration of the RPE. As the RPE cells perform a nourishing role to the highly metabolic photoreceptors by providing growth factors, removing waste, and recycling essential compounds, loss of the RPE ultimately leads to photoreceptor failure and loss.

Due to the central role of RPE in the development of AMD, replacement of the aging RPE under the macula has long been postulated to be a worthwhile strategy to treat the disease. In AMD patients presenting with sudden onset of profound vision loss, good visual outcomes have been achieved by surgical transposition of autologous peripheral RPE under the macula. While these procedures had encouraging results in terms of visual outcomes, the operations were long and technically challenging. Additionally, the complication rates were significant, and so overall, these procedures were not suitable for routine use.[3] An alternative to the transplantation of autologous RPE is the transplantation of RPE from an exogenous source without the need to harvest it intraoperatively. Techniques for doing this have been pioneered by many research groups. The source of exogenous cells has moved from using fetal tissue through adult cadaveric donor tissue, and more recently, toward stem cells in their various guises.[4]

New RPE-Based Therapies

Currently three groups have reported performing transplants with RPE derived from pluripotent stem cells in AMD. In California, Ocata Therapeutics (formerly ACT) was the first to transplant RPE cells derived from human embryonic stem cells (HESC) into patients with advanced dry AMD as well as in patients with Stargardt's disease. The cells were injected as a suspension into the subretinal space, and the results for nine AMD patients have been published with no evidence of rejection or tumor.[5] These are encouraging first results for cellular therapy in AMD as they suggest that HESC may well be a safe cell source for transplantation.

Researchers at the Riken Centre in Japan reported in 2014 that they had transplanted stem cell–derived RPE into a patient with AMD. The source of the stem cells for this trial was induced pluripotent stem cells (IPSC) derived from the patient's own skin. The RPE was transplanted as strips rather

than as a suspension. This is the first IPSC trial worldwide, and the results are eagerly awaited.

The third group, the London Project to Cure Blindness in partnership with Pfizer Neusentis, has reported that it has performed a first transplantation into a patient with recently diagnosed wet AMD. As with the ACT trial, the source cells were HESC. However, in contrast to that study, the cells were transplanted as a monolayer "patch" on a coated polymer sheet as a replacement for Bruch's membrane. This patch sits under the retina, covering nearly the entire macular area.

Many other groups across the world are carrying out or planning trials for AMD using a variety of other techniques and cell types, including those derived from umbilical cord, fetal brain, and bone marrow.[6]

Predicting Success

In developing these new cellular therapies, often termed advanced therapy medicinal products (ATMP), we are not just facing new challenges at the bench and in the clinic; we are dealing with multiple regulatory bodies, which are themselves interpreting new and recent legislation.[7] The novelty of cellular therapy has added a regulatory stringency that acts to drive up standards. However, the level of scrutiny also drives up the cost of new therapy translation, which in many cases is being shouldered by industry partners, and these costs must be justified. Although a complex ATMP is initially developed at one center, it has to be trialed eventually in multiple centers. This is to exclude the possibility of the outcome's being driven by a particular, local factor that may reduce the efficacy when the product is distributed more widely. Furthermore, the production of the cells in a cellular therapy needs to be scaled up and potentially delivered to the patient cohort worldwide. All of these steps necessarily escalate the costs, and this plays a significant role in defining the rate of progress of new treatments. In the field of RPE patch production, efforts are currently under way to mechanize the production process, not only to address cost but also to match the potential patient numbers and standardize manufacturing consistency and quality control issues.

Advanced therapy medicinal products have used the regulatory and development pathway of conventional molecular pharmacology agents as the model for development of new therapies. Implicit in this is the understanding that less than a third of drugs make it from stage 1 clinical trial to Food and Drug Administration approval.[8] The actuarial process of predicting which treatments will ultimately be successful is ever more rigorous due to the substantial costs of taking new treatments to the market. To help anticipate what has a better chance of making a difference to patients with AMD we can engage the concept of "stratified medicine." This involves understanding disease subtypes with a view to predicting their response to a treatment. With new understanding of the genetic background of AMD and the ever-improving ability to image the retina and macula, this stratification is possible in AMD.[9]

In terms of AMD subtypes, it is only the late form of the disease that is being targeted at present due to the undefined risks of cellular therapy. Although most groups working on cellular therapy plan to treat dry AMD, the early trials are being carried out on both wet and dry disease. In RPE transplantation for late-stage dry degeneration, assessment of visual outcome is not possible as there is already photoreceptor loss. However, studies in late dry AMD still prove very useful in terms of toxicology and monitoring for tumor safety while informing us about graft survival and immune reaction. Conversely, in early wet AMD, the decline in vision happens suddenly, with the photoreceptors initially relatively unaffected. Treatment at this point with RPE transplantation may restore vision. At a certain point in time, however, if left untreated, the wet AMD progresses to scarring, retinal damage, and permanent visual loss. There is thus a therapeutic window in which to intervene. Trialing cellular treatments in wet AMD allows the assessment of visual outcome as well as cell survival and safety. Thus targeting the wet subtype will likely yield the most useful information in the first instance. However, recruitment is more difficult, as this subgroup represents the smaller cohort of patients.

Defining Success

Three areas are important in documenting the level of success in cellular therapy. These are safety, cell survival, and visual outcome. First, and most important, is demonstration of safety. For cellular therapy the major safety concern has been the development of tumors in the transplanted cells. As such, these therapies have been meticulously characterized and observed following transplant into animals in preclinical trials to ensure that no such transformation has occurred. Other potential toxic effects include a strong immune response to the cells, which could reduce vision or cause pain. Additionally, there are possible operative complications.

After safety risks have been addressed, the next outcome issue peculiar to this field is whether the cells survive following transplantation. Even if a florid immune reaction is avoided, there is still a possibility over time that the cells would be lost to other mechanisms including attack from macrophages resident in the retina. Predicting the level of immunosuppression that is necessary to protect allogenic sources has been central to planning trials. It is possible that human leukocyte antigen matching will be useful, but this has not been examined in a trial to date. Monitoring cell survival in the eye is slightly easier due to its transparency. If the new cells can be localized, especially if present as a monolayer, they can be observed directly and measured by new and detailed retinal imaging systems and their survival or loss accurately determined and documented.

The ultimate measure of success in any retinal transplant, of course, comes in the form of an improvement in measurements of retinal function. These tests include the electroretinogram, which analyzes the basic electrical activity of the retina, perimetry to test the visual field, and most importantly visual acuity. The aim of treatment is ultimately for patients to report an improvement of their symptoms and return to reading and enjoying and engaging in their normal visual world.

Next Steps

The advent of cellular therapy for AMD and the translation of laboratory-based stem cell treatments into early clinical trials represent a completely novel way to address AMD. Following these first clinical trials, we are beginning to understand cell-based techniques, artificial substrates, and methods of delivery. We are also beginning to see how healthy cells rescue function and arrest disease progress. At present this work is centered on RPE replacement, leaving a significant group of patients who have already lost photoreceptors and therefore need a more sophisticated therapy. This group could potentially be treated in the future using cells differentiated to photoreceptors in addition to an RPE transplant.

Feedback from the early trials will also inform how to adequately tackle the immune response to the grafts and whether local immune therapy is enough or if systemic immunosuppression is also warranted. With the advent of IPSC techniques, autologous sources may offer an immunologic advantage, though it may still be desirable that HLA-matched

Investigative Ophthalmology & Visual Science

banks of RPE be available in order to treat patients in a timely manner during the therapeutic time frame with minimal chance of rejection.[10] With a current lag time from skin to RPE of many months, IPSC is unlikely to be beneficial for patients with wet AMD but might be a sound option in the future for patients with more slowly progressing disease such as dry AMD. The advent of IPSC has also led to the development of patient-specific disease models that will likely herald a new era in the understanding of and therapeutics for many retinal degenerations including AMD.[11,12]

The commencement of clinical trials in the field of cellular therapy for AMD represents the culmination of many years and many strands of preclinical research. New cellular techniques, advances in biocompatible compounds,[13] a revolution in retinal imaging, and surgical advances in the delivery of cells have all played their part. From the outset AMD has been a good target, partly because of the enormous burden it presents to the community but also because of the early involvement in a relatively localized cell layer and portion of the retina that is potentially treatable. Finally, however, the most important feature may yet be that AMD sufferers are a highly motivated and powerful lobby, many of whom are retired, with time to engage with their disease. Their diligent involvement in the clinical trials process may well be significant to fulfill the promise of cellular therapy and regenerative medicine as one of the most important medical advances of our time.

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