Gene therapy for retinopathy of prematurity: the eye is a window to the future

The eye is the window to the brain, the soul, and now perhaps even the future, with the exciting publication by Chowers et al in this month’s issue of the *BJO* (p 991). The authors give us a view of the future as they elegantly demonstrate that gene transfer into blood vessels is possible in a rat model of retinopathy of prematurity (ROP). The future may be close at hand, because the eye once again offers an ideal organ to study the effects of this new therapy. ROP, a developmental disease of retinal angiogenesis in premature infants, is also an optimal and important disease to study potential therapeutic effects of gene therapy.

To date, the view of future gene therapy has been through hazy media at best. Despite incredible advances in developmental biology and molecular genetics during the past several decades, efforts to utilise these advances, and to deliver therapeutic genes to target organs or structures, have often been disappointing. The reason for disappointment usually hinges on delivery and expression of the therapeutic gene to the desired target. A vector must be used, one that transports a gene or genes to the target. The vector should be innocuous, sustainable, and, of course, able to deliver a genetic sequence that can be inserted into target cells’ DNA. Thus the vector also must be able to cross cell membranes and survive an environment that eschews anything foreign. While outside the cell, the vector must be able to survive the host’s immune system. It is this latter issue—the host immune system—that arguably poses the most formidable challenge to gene therapy. Viral vectors used for gene therapy are quickly recognised by the host immune system and eradicated.

With current technology, the ideal disease to study gene therapy should be developmental (occurring only during a short time period) and should occur in an immunologically privileged part of the body. ROP is one such disease. It occurs during a narrow window of time—the length of time from the onset of pathological neovascularisation to devastating retinal detachment is usually measured in weeks. Even if a viral vector only survives a few days or weeks, it still could effectively provide genetic material long enough to affect the disease. And ROP occurs inside the eye where the immune system is relatively inactive. Clearly, the authors have chosen a disease where gene therapy has a fighting chance to succeed.

ROP is also a disease in need of better therapy. It occurs in premature infants and remains a leading cause of vision impairment in children. Advances in neonatology allowing survival of the smallest infants contribute to the incidence of ROP. Although cryosurgery and laser retinal ablation of avascular retina improve chances of a favourable outcome, approximately 30% of infants with threshold ROP experience a retinal detachment and blindness. More than 80% of infants who develop threshold ROP develop visual acuity of 20/40 or worse, and even when the retina remains attached. Other blinding eye diseases are also caused by pathological neovascularisation, including diabetic retinopathy and age related macular degeneration.

Gene therapy mediated regulation of cytokines and growth factors known to be involved in ROP would be a promising approach if proved to be feasible in animal models. Cytokines such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and insulin-like growth factor (IGF-1), hypoxia inducing factor (HIF-1), and angiopoietin 2 may have roles in ROP. Therefore, the targeting and regulation of such factors by gene therapy is a realistic goal for developing newer and better ROP treatments. In their studies, Chowers et al tested retrovirus, adenovirus and herpes virus based vectors, shuttling a β-galactosidase reporter gene for expression in retinal blood vessels in rodents undergoing oxygen induced retinal neovascularisation. Interestingly, they found that adenovirus offered the best efficiency in expression in retinal blood vessels compared with all the other vectors. Moreover, the adenovirus expression was specific to the blood vessels of the inner retina and did not appear to be expressed in the deeper neural retina.

These studies indicate that adenoviral vectors can be expressed in retinal blood vessels and therefore may provide a feasible means for shutting genes of interest into retinal blood vessels undergoing neovascularisation. They also suggest that adenovirus can be targeted to specific areas of the eye, and might then minimise non-specific effects through collateral tissues.

Non-specific effects could be very problematic even when collateral tissues are not directly affected by gene therapy. Somehow, gene therapy for ROP will have to limit pathological retinal neovascularisation while permitting the normal process of retinal angiogenesis. The sequence of molecular events leading to development of blood vessels is complicated, with some effects of cytokines occurring at more remote ocular sites. In fact, ROP is more
than simply a disease of retinal angiogenesis. Myopia is more common, visual acuity is usually diminished, and cicatricial changes brought about by the ROP disease process may lead to glaucoma.

Here the view of future gene therapy for ROP becomes obfuscated. Future researchers must carefully avoid these collateral effects and should consider the developmental nature of the disease. It would be a tragedy to halt pathological neovascularisation only to find additional, unwanted, downstream effects such as altered photoreceptor cell development or downregulation of factors that contribute to healthy blood vessel formation, such as pericyte growth and survival. The future requires more basic science work. Until we know more detail about the molecular events that cause ROP, and their timing, it will be unsafe to intervene in human ROP. In neovascular diseases occurring in mature systems—for example, diabetic retinopathy, the future could be closer.

The advance reported in the BJ O this month moves us closer to a better treatment for neovascular eye disease. It is now possible to see shape and form in the future, but details remain obscure. We could well have a method to deliver genes to retinal vessels, but we need to learn which genes to deliver and when to deliver them, before embarking on treatment of human disease. This much is very clear: gene therapy has a future in blinding eye disease. Adenovirus vectors appear to effectively transfer genes into blood vessels in the eye.

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Optic disc changes following trabeculectomy

The reversal of optic disc cupping following pressure reduction by medical or surgical means has long been recognised, particularly in congenital and juvenile glaucoma. Less clear cut is whether this reversal is accompanied by any improvement in visual function. The matter is, obviously, an important one and there are some reports suggesting that an improvement may occur. If so this presumably is due to recovery of neuronal function which has only temporarily been interrupted. Although it is of great importance to know how extensive this process may be, only studies conducted with great care and rigour are likely to tell this conclusively.

The precise pathological mechanism underlying any reversal is also important. Presumably there is reversal of bowing of the lamina but definitive proof of this is difficult. If there is in fact any recovery of function this may be due to a neuronal change although it is doubtful how this would occur, except by reversal of changes which are still transitory.

In a paper in the current issue of the BJ O (p 956), Kotecha and coworkers have attempted to solve some of these contentious problems. They have identified “significant” increases in rim volume at 2 years following surgical operations which produced a fall in pressure of around 30%. Some change in maximum cup depth was demonstrated. This was “significant” at 1 year but not at 2 years. The changes seem small. A change in rim volume suggests something more than just a lessening of bowing of the lamina. Although all patients had 24-2 threshold Humphrey visual field tests, no results of these are given so there is no comment regarding visual function. Perhaps a later paper will tell us more.

The results given hardly seem likely to be the basis for much recovery of lost visual function in glaucoma but they do suggest that a reduction in intraocular pressure to the low normal range will halt the glaucomatous process evident at the optic nerve head. However, it may still be too early to paraphrase the slogan of a recent US presidential election “It’s the economy stupid” to “It’s the pressure stupid.”

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The income that we get from resource-poor countries is minimal; and facilitating information supply should encourage development, improvement in health care, and eventually create a market.

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The challenge will be sustainability. It is easy for donors to invest money and reap the rewards of short term success. But enhancing information flow will have no impact on health if projects continue only as long as their funding lasts. Information cannot be separated from the capacity of a healthcare system to work effectively over time. How is it possible to influence the context within which information will flow, the apparently intractable political, economic, and organisational constraints that disable rather than enable information to work for people?

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