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Cover Story

Cornea-targeted gene therapy using adenovirus vector

There are few therapies that catch the eyes of the public more than improving sight in the visually impaired. Cell and gene transfer approaches have made preclinical and clinical headway in this domain. Gene transfer to the retina has received the most attention in recent years, culminating in the promising results for Leber congenital amaurosis, a hereditary congenital blindness due to a breakdown of the visual cycle. The encouraging results in retina disease therapy provide a significant impetus and are clearing a path for clinical trials for cornea therapy. When one looks in the mirror there are two organs that are most readily at the surface and visible: the skin and the cornea. Corneas are very accessible, small and enclosed compared with many other organs, and avascular, which sequestrate them from the circulation. Among the three primary cell types in the cornea, the keratocyte (different from the ubiquitous keratinocytes) and endothelial cells would make logical targets for the risks and costs associated with gene transfer. Under normal conditions a keratocyte is a very long-lived cell in humans, with an estimated time of up to two years — similar to that of hepatocytes. The epithelial cells have a rather rapid turnover and therefore would need regular interventions essentially precluding them from classic gene transfer approaches.

In this issue, Serratrice and colleagues describe their cornea gene transfer results using a novel gene transfer platform based on helper-dependent canine adenovirus type 2 (CAV-2) vectors [1]. This nonhuman helper-dependent adenovirus vector has a handful of characteristics (high efficacy and cloning capacity, low immunogenicity) that makes it attractive for gene transfer in humans. Another strength of this study is that the team used corneas from four genera: the traditional and ubiquitous laboratory mouse, man's best friend (dog), an interesting nonhuman primate (gray mouse lemur), and human. The gray mouse lemur is a particularly unique animal that has the capacity to circumvent some of the practical and ethical challenges associated with working with nonhuman primates traditionally captured in the wild. The outbred primate can be readily bred in captivity, live for up to fifteen years and has a number of other characteristics interesting for translational research. The mucopolysaccharidosis type VII (or Sly Syndrome) dog used in this study also allowed the authors to test the ability of CAV-2 vectors in a pertinent disease that closely mimics the pathology in humans based on the cornea size and pathophysiology. MPS VII is caused by a deficiency in β-glucuronidase activity, which leads to glycosaminoglycan and ganglioside accumulation. The French and American collaborators achieved the goal of corrective therapy, i.e., the steady controlled release of β-glucuronidase and its diffusion throughout the collagen-dense stroma, demonstrating the usefulness of CAV-2 vectors for modifying corneal keratocytes.

While Serratrice and colleagues have made a notable step forward, there are, as always, avenues that could be taken for further improvement: long-term controllable expression, further reducing the dose by improving production parameters, improving biodistribution in the dense collagen matrix of the cornea stroma, possibly transducing the stem cells that repopulate the stromal keratocytes and eliminating the production of the endogenous and defective β-glucuronidase (e.g. via siRNA) which would have a dominant-negative affect on the tetrameric enzyme. These improvements to be made are not trivial and will take time. Since the first attempt of the gene therapy on a human several decades ago, this seemingly simple idea has had a difficult time producing a clinically useful gene therapy product. There have been more than 1800 gene therapy clinical trials, but no product has been approved by the Food and Drug Administration. Either safety and/or efficacy have not been proven for any of the studies. For any gene therapy to work, effective gene delivery systems that allow transfection of target cells and sustained expression of the transfected genes will be the key. It seems that the gene delivery systems have not yet matured enough to achieve the ultimate goal of gene therapy. Zero success out of more than 1800 trials is something that scientists should ponder seriously. Certainly, successes with *in vitro* petri dishes and small animal models are far from clinical success. This brings a question: are scientists biased for their own gene delivery systems? It is a good time to establish certain criteria that can be used to check whether a given gene delivery system may have any chance of success in clinical trials.

Reference

[1] N. Serratrice, A. Cubizolle, S. Ibanes, N. Mestre-Francés, N. Bayo-Puxan, S. Creyssels, A. Gennetier, F. Bernex, J.-M. Verdier, M.E. Haskins, G. Couderc, F. Malecaze, V. Kalatzis, E.J. Kremer, Corrective GUSB transfer to the canine mucopolysaccharidosis VII cornea using a helper-dependent canine adenovirus vector, J. Control. Release 181 (2014) 22–31

Kinam Park
Purdue University
Departments of Biomedical Engineering and Pharmaceutics
West Lafayette, Indiana, USA
E-mail address: kpark@purdue.edu

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