

23rd INTERNATIONAL CONGRESS OF GERMAN OPHTHALMIC SURGEONS

DOC October 21st – 24th, 2010 **DOC**
Congress Center Hamburg



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OCTOBER 21ST AND 22ND, 2010

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- Vitreoretinal surgery
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Update

CORNEA

CORNEA GENE THERAPY

Experimental applications are promising

by Howard Larkin in Boston

The cornea presents unique opportunities and challenges for gene therapy with potential applications ranging from treating dystrophies to reducing haze after surface ablation, reported Mark Rosenblatt MD, PhD at the Sixth World Cornea Congress.

Experimental applications are promising, but further investigation of the molecular mechanisms of corneal disease and development of improved animal models are necessary to move forward, said Dr Rosenblatt, Weill Cornell Medical College, New York.

“You can add a gene to express more of a protein. Theoretically you can excise a bad gene and replace it with a new one. A more recent technique is to use small inhibitory RNAs to create functional knock-outs. We don’t remove the gene but use special genetic elements to turn off the expression of the defective gene. I think this is going to be very important to treat many of the dystrophies in the cornea,” he said.

Genes can be inserted through viral or non-viral vectors. Retroviral, lentiviral and adeno-associated virus vectors insert their DNA into the target cell DNA, and are expressed over the long term. Adenovirals are more transient, as are non-viral vectors, such as liposomes and naked DNA. Non-viral vectors tend to be less efficient in transferring genetic material, though transfer rates are improving.

As far back as 1990, gene therapy was used in treating severe combined immunodeficiency (SCID) with apparent success, Dr Rosenblatt said. But gene therapy did not enter routine clinical use because there also have been serious failures. These include an 18-year-old patient dying in 1999 likely due to a high dose of adenoviral vectors to which he was susceptible. Also, in the early 2000s some of the patients treated for SCID early on developed lymphoma, he noted.

Still, gene therapy has many potential applications and the eye is an attractive location. For one, the eye is very accessible and is a separate compartment, making it possible to test gene therapy in minute quantities that reduce the risk of systemic reactions.

Applications for retinal disease are more advanced. A gene therapy for Leber congenital amaurosis is in human trials with early success in restoring vision. It was

developed in a canine model with the dog Lancelot literally becoming the poster animal for gene therapy research, Dr Rosenblatt said. Unfortunately, no similar models are available for corneal disease. “Having this large animal model available is one reason why retinal gene therapy has progressed quicker than corneal gene therapy.”

Nonetheless, many corneal gene therapy approaches are possible or in development. Dystrophies are good candidates. But specific gene therapies have not yet been developed despite the discovery that one gene is responsible for many corneal dystrophies.

“We don’t even know the cell types involved and we have a poor biochemical understanding of what causes the dystrophy. Is it a gene deficiency? Likely not; it is probably dominant negative, meaning abnormal protein is interacting with normal protein that then leads to the phenotype. It has been very difficult to develop animal models for these dystrophies.”

Also, the genes responsible for some common conditions, such as Fuchs’ and keratoconus, have not yet been discovered.

Stable viral vectors would be best for treating dystrophies because these are lifelong conditions, Dr Rosenblatt added.

Another potential target for corneal gene therapy is graft rejection, which is a significant problem following penetrating keratoplasty. However, there are multiple immune pathways to rejection and multiple triggers for rejection, including neovascularisation and infections.

“The approach needs to be to the critical pathway to immune modulation, but really what is the master regulator; probably there is no single one for each patient.”

An approach might involve identifying and prioritising pathways and targeting them with long-acting vectors. The therapy could be applied ex vivo using donor transplant tissue or in vivo using injections.

Laser refractive surgery is another potential target. Despite submicron precision of excimer lasers, refractive surgical outcomes are not entirely predictable, and surface ablation can lead to corneal haze, Dr Rosenblatt said. One goal would be to make keratocytes more quiescent and reduce haze formation.

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