Gene therapy to rescue vision: From bench to bedside
Sunday, May 01, 2016 5:15 PM–7:15 PM
6ABC Symposium
Program #/Board # Range: 1332–1336
Organizing Section: Nanotechnology and Regenerative Medicine Group
Contributing Section(s): Anatomy/Pathology, Biochemistry/Molecular Biology, Cornea, Genetics, Glaucoma, Lens, Physiology/Pharmacology, Retina

Program Number: 1332
Presentation Time: 5:15PM–5:39PM

The state of gene therapies
Wilson Bryan1, 2. 1Office of Cellular, Tissue, and Gene Therapies, FDA, Silver Spring, MD; 2Office of Cellular, Tissue, and Gene Therapies, CBER, Silver Spring, MD.

Presentation Description: This presentation describes the current state of gene therapies, from the perspective of the Director, Division of Clinical Evaluation and Pharmacology / Toxicology, Office of Cellular, Tissue, and Gene Therapies (OCTGT), Center for Biologics Evaluation and Research (CBER), United States Food and Drug Administration (FDA). Topics covered include regulatory perspectives on the challenges and successes that have been seen with gene therapies for a variety of indications, including ophthalmologic disorders.

Commercial Relationships: Wilson Bryan, None

Program Number: 1333
Presentation Time: 5:39PM–6:03PM

Design, Validation, and Translation of AAV Gene Therapy Vectors for the Treatment of Ocular Diseases
Matthew Hirsch1, 2. 1Ophthalmology, University of North Carolina, Chapel Hill, NC; 2Gene Therapy Center, University of North Carolina, Chapel Hill, NC.

Presentation Description: This presentation intends to provide an overview of the bench to bedside journey using adeno-associated virus (AAV) vectors for the treatment of genetic diseases with a particular focus on ocular abnormalities. Topics will include the design of AAV transcriptional cassettes, the choice of AAV capsids for specific tissue/cell transduction when administered by different routes, and other emerging trends towards safe and efficient AAV-mediated gene delivery in the eye. Next, validation of the chosen reagents will be addressed including efficacy and toxicity experiments necessary for FDA approval and other ethical obligations. Finally, a brief overview of negotiating the regulatory obstacles will be discussed. Throughout this presentation, our experience with these aspects for the development of AAV gene therapy for a corneal disease will used as an example to illustrate/highlight the considerations of each step in the process.

Commercial Relationships: Matthew Hirsch, None

Program Number: 1334
Presentation Time: 6:03PM–6:27PM

Allotopic Gene Therapy for ND4 Leber Hereditary Optic Neuropathy with rAAV2/2-ND4 (GS010): From Pre-Clinical Development to Phase III

Presentation Description: Gene therapy has come of age. Treatment of hereditary causes of vision loss is now feasible. The anatomy and physiology of the eye is conducive for the delivery of gene therapy treatments to the neural cells of the retina. Allotopic expression utilizes the nuclear machinery for expression of mitochondrial encoded proteins. Adeno-associated viral vectors have been shown to be safe for use in the eye. Drug development in rare disease includes unique challenges requiring global strategic development and interaction with regulatory agencies is vital and should begin at early stages.

Leber Hereditary Optic Neuropathy (LHON) is a rare mitochondrial genetic disorder primarily affecting young males. Affected patients experience bilateral severe central vision loss. Currently no therapy is approved in the United States to prevent, halt or reverse vision loss due to LHON.

GS010 is a recombinant adeno-associated viral vector, serotype 2, carrying the wild-type ND4 gene (rAAV2/2-ND4) and is an experimental gene therapy for the treatment of LHON due to the G11778A ND4 mitochondrial mutation. GS010 has received orphan drug designation in EU & USA. GS010 contains a Mitochondrial Targeting Sequence (MTS) that allows localization of the wild-type protein to the mitochondrion, enabling restoration of mitochondrial function.

A Phase I/IIa safety and tolerability study of GS010 has completed recruitment. Systemic safety is excellent. No unexpected adverse events occurred. Local (ocular) tolerability is good with side effects that are responsive to and resolve with standard therapy. Trends of efficacy in improving vision have been detected in the safety study despite the relative chronicity of disease in a majority of the included patients.

Regulatory approval to initiate Phase III efficacy studies have been received. The RESCUE and REVERSE Phase III studies of GS010 will be conducted in the United States and some European Union countries. RESCUE and REVERSE are randomized, double-masked, sham-controlled trials and will collectively include patients up to one year after the onset of vision loss.

Commercial Relationships: Scott Uretsky, GenSight Biologics
Clinical Trial: NCT02064569

Program Number: 1335
Presentation Time: 6:27PM–6:51PM

Mitochondria targeted gene therapy for Leber Hereditary Optic Neuropathy (LHON)
John Guy. Bascom Palmer Eye Institute, Miami, FL.

Presentation Description: Our laboratory has developed techniques and animal models directed towards treating patients with visual loss from Leber hereditary optic neuropathy caused by the G11778A mutation in mitochondrial DNA. Since there had been no way to import DNA into the mitochondria we adopted an approach coined “allotopic expression” for the nuclear approach.

For the nuclear approach we used the allotopic technology of recoding a mitochondrial gene in the nuclear genetic code and redirecting the cytoplasmically synthesized protein to the mitochondria. This was necessary because the technology to introduce DNA to mitochondria did not exist. Recoding the ND4 gene was necessary because using the mitochondrial gene specifying the ND4 subunit of complex I expressed in the nucleus and cytoplasm would result in a short polypeptide of approximately 10 amino acids as the TGA encoding for tryptophan in the mitochondria is a stop codon in the nucleus. The ND4 protein is composed of 340 amino acids. This approach is now in phase I clinical trials.

We later developed an entirely independent way to express genes in the mitochondria by developing the technology to actually import DNA into mitochondria. Vector production targeted to the mitochondria utilizes a modified AAV (VLP2) capsid into which a mitochondrial targeting sequences is added to the viral shell to deliver its gene a normal ND4 into the mitochondria. Translation is driven by a mitochondrial heavy strand promoter (HSP). Using this technology we developed transgenic mice expressing the mutant...
G11778A ND4 and reversed visual loss with injection of the wild-type allele. Our gene therapy approaches may some day prove useful to LHON patients.

**Commercial Relationships:** John Guy, inventor (P)

**Clinical Trial:** Clinicaltrials.gov number: NCT02161380

**Program Number:** 1336

**Presentation Time:** 6:51 PM–7:15 PM

**Ocular gene therapy: Clinical successes and lessons learned**

Jean Bennett1, 2. 1Center for Advanced Retinal and Ocular Therapeutics, University of Pennsylvania Scheie Eye Institute, Philadelphia, PA; 2Center for Cellular and Molecular Therapeutics, The Children’s Hospital of Philadelphia, Philadelphia, PA.

**Presentation Description:** Gene therapy has the potential to reverse disease or prevent further deterioration in patients with incurable degenerative diseases. The demonstration of safe and stable recovery of retinal/visual function in children and adults with congenital blindness due to RPE65 mutations in gene therapy trials being carried out at The Children’s Hospital of Philadelphia (CHOP) and at the University of Iowa provide great hope for people with other more common blinding diseases. The CHOP Phase 1-2 study is now >8 years past initiation and the multi-center Phase 3 (pivotal) trial is well underway. The latter study is the first randomized controlled Phase 3 gene therapy trial for genetic disease of any kind. The first set of results from the Phase 3 studies revealed robust improvements in retinal and visual function and in functional vision as well as a high degree of safety, thereby placing the recombinant adeno-associated virus reagent (AAV2-hRPE65v2) as the frontrunner for being the first approved gene therapy drug in the USA. This presentation will describe the challenges presented by the nature of the targeted disease itself, decisions that were made at various junctures of the studies and the modifications that were made in response to clinical findings. The net result is a path that can be adapted for future ocular gene therapy studies.

**Commercial Relationships:** Jean Bennett, Spark Therapeutics (F)

**Clinical Trial:** NCT00516477, NCT01208389, NCT00999609

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