RETINITIS PIGMENTOSA: NOVEL TREATMENTS AND CHALLENGES

Organizers: Ygal Rotenstreich, MD and Ifat Sher, PhD

Retinitis pigmentosa (RP) is the fourth most common cause of blindness in the industrial world. Currently, there is no known cure for RP. The course will highlight promising innovative treatments that have been emerging in recent years from translational research into clinical trials, including stem cell therapies, gene therapy, CRISPR genome engineering, nutritional interventions and retinal prosthesis systems. New sensitive imaging techniques and functional assays will be presented that may improve patient screening for clinical trials and enable better evaluation of treatment safety and efficacy. The course will use the platform to discuss the means for successful application of preclinical research findings into clinical trials.

1-1:05pm
Welcome and introduction
Ygal Rotenstreich, MD, Goldschleger Eye Research Institute, Tel Aviv University, Sheba Medical Center

Following a short welcome to moderators, speakers and audience, a brief introduction on retinitis pigmentosa and the main aims of the course will be presented. These include updating the research and medical community regarding the development of new treatments for the disease, as well as strategies for bridging the gaps between laboratory translational research findings and successful clinical trials.

1:05-1:25pm
Outcome measures for clinical trials in patients with inherited retinal degenerations
Mark Pennesi, MD, PhD, Casey Eye Institute, Oregon Health & Science University

Accurate and repeatable diagnostic testing is imperative to assess outcome measures in the growing number of clinical trials for inherited retinal degenerations. This presentation will review current methods such as perimetry, electrophysiology, and imaging; and the role the can play in clinical trials.

1:25-1:45pm
Nutritional interventions for inherited retinal diseases
Paul S. Bernstein, MD, PhD, Moran Eye Center, University of Utah School of Medicine

Our current paucity of effective interventions against inherited retinal diseases is a source of significant frustration for both patients and physicians. It is therefore common for these patients and their families to inquire whether changes in diet or consumption of supplements could alter the course of their disease. Fortunately, as our knowledge of biochemical and genetic mechanisms of inherited retinal diseases increases, there are indeed indications that selected nutrients might have beneficial effects, but there is considerable misinformation as well. In this presentation, I will review the basic and clinical science underlying potential nutritional interventions against inherited retinal and macular dystrophies with particular emphasis on retinoids, carotenoids, antioxidant vitamins, and polyunsaturated fatty acids, and I will provide an overview of future directions of retinal nutrition research for these inherited disorders.

1:45-2:05pm
Objective Visual Field and 9-cis Beta-Carotene Treatment for Retinitis Pigmentosa
Ygal Rotenstreich, MD, Goldschleger Eye Research Institute, Tel Aviv University, Sheba Medical Center
The clinical trial methodology is key for a successful clinical trial. The double masked crossover design of the clinical trial of 9-cis beta carotene treatment for retinitis pigmentosa will be discussed, as well as the promising results demonstrating improvement in retinal and visual function in one third of the patients. These clinical studies led to the development of an objective outcome measure for retinitis pigmentosa clinical trials: an objective perimetry based on pupil responses to chromatic (red and blue) light presented in different locations of the visual field. A comprehensive analysis of pupil response kinetics may enable differential diagnosis of various blinding diseases, monitoring disease progression and evaluation of the safety and efficacy of new treatments for retinitis pigmentosa in clinical trials.

2:05-2:25pm

**Strategies for genetic screening in patients with inherited retinal dystrophies**

*Tamar Ben Yosef, PhD, Technion Israel Institute of Technology*

Inherited Retinal Diseases (IRDs) are a heterogeneous group of visual disturbance diseases caused by hundreds of different gene defects, mainly affecting photoreceptor cells. To date, over 250 genes have been associated with different IRD phenotypes. Identifying the genetic cause of disease in IRD patients is highly important for two main reasons: First, it allows molecular diagnosis and genetic counseling. In addition, it is crucial for development of novel therapeutic approaches. The increasing list of known genes underlying IRD can be classified into several groups, based on their functional protein products. Therefore, both gene-based and non-gene based therapies will have to be tested on a set of patients with a known genetic diagnosis to prove their efficiency. There are several available diagnostic approaches for IRD patients. Sanger sequencing of specific IRD – causative genes can sometimes be performed, but given the large number of relevant genes, this approach is usually not effective. The Arrayed Primer Extension (APEX) technology allows simultaneous detection of hundreds of previously-reported DNA alterations in many different genes. Currently, the most effective strategy for identifying the genetic basis for disease in these patients is next generation sequencing, including Whole Genome Sequencing (WGS), Whole Exome Sequencing (WES), and Targeted Next Generation Sequencing (TNGS). The pros and cons of each strategy, as well as factors to be considered during data analysis, will be discussed.

2:25-2:40pm – Break

2:40-3:00pm

**Stem cell therapies for the treatment of retinal degenerative diseases**

*David M. Gamm, MD, PhD, McPherson Eye Research Institute, University of Wisconsin-Madison*

Pluripotent stem cells have received a great deal of attention over the past two decades due mainly to their potential to serve as an unlimited source of cellular “replacement parts” for a host of incurable degenerative diseases. For many reasons, the eye has led the way in the development and testing of human stem cell therapies, and clinical trials are now underway. This presentation will focus on recent advances and remaining challenges in the effort to restore vision using stem cell technology.

3:00-3:20pm

**Gene therapy for hereditary retinal diseases**

*Eyal Banin, MD, PhD, Hadassah-Hebrew University Medical Center*

The eye, and in particular retinal diseases, have recently become the “testing ground” for many novel therapeutic modalities. This presentation will focus on the development and application of gene augmentation and gene manipulation to treat hereditary retinal diseases (HRDs). Following a short introduction on the complexity of HRD genetics, I will attempt to provide our experience in this field as an example to the opportunities afforded as well as challenges presented by gene augmentation therapy. This will include data from our small Phase I clinical trial in patients with LCA caused by mutations in the RPE65 gene, as well our attempts to develop gene augmentation therapy for CNGA3 achromatopsia in a large animal model of the disease. An overview of current clinical gene therapy trials that are being conducted throughout the world will then be presented, with emphasis on RPE65 which may soon be the first FDA-approved gene augmentation treatment, as well as the trials addressing choroideremia, retinoschisis, MYO7A Usher1 syndrome, ABOCR-related disease, Mertk mutations, CNGB3 and CNGA3 achromatopsia, and others. Novel approaches beyond the use of viral vectors, such as gene editing using CRISPR technology, translational read-through drugs, and also the use of gene delivery to express modulating factors rather than correct the causative mutation, will be presented in brief. Finally, questions and emerging challenges related to gene therapy will be pointed out, including the practical difficulty in developing separate treatments for a large number of different genes (each
causing disease in a relatively small number of patients), the complexity of identifying outcome measures and treatment effects in slowly progressive diseases, the need to find ways to treat larger areas of the retina (such as by intravitreal rather than by subretinal delivery), immune response to the vectors as well as possible toxicity of the expressed protein, and the possibility that the treatment may not arrest disease progression and may diminish over time. In conclusion, the need to strive for a molecular genetic diagnosis in all our HRD patients will be stressed, both with regard to the possibility to use this knowledge to prevent transmission of disease within the family as well as the potential that in some of the cases, this may allow application of corrective gene therapy.

3:20-3:30pm
**CRISPR/Cas technologies for genome and epigenome editing**
*Albert W. Cheng, PhD, The Jackson Laboratory for Genomic Medicine*

An overview of current state and the future directions of CRISPR/Cas technologies and their applications in editing of the genome and epigenome, in basic science, industry and therapeutics will be presented.

3:30-3:40pm
**Clinical Implementation of Gene Supplementation and Genome CRISPR-surgery in RP**
*Stephen Tsang, MD, PhD, Edward S. Harkness Eye Institute, Columbia University*

Inherited genetic disorders of the eye result in severe health effects in patients and to date many of these disorders have been intractable to precise therapies. Since the first efforts to sequence the human genome, scientists and physicians have aimed to modify pathogenic genomic loci to alleviate disease burden. Recently, with the advent of technologies for direct DNA modification, practicing precision genome surgery in the ophthalmology has become closer to reality. Originally derived from the immune system of bacteria and archaea, Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-CRISPR-associated (Cas) systems have become an essential tool for genome surgery.

3:40-4:00pm
**Argus II clinical trial update**
*Mark S. Humayun, USC Roski Eye Institute, Keck Medicine of USC*

My presentation will be about the five-year results of the Argus II Retinal Prosthesis Study. As of January 1, 2016, 30 subjects have been implanted at 10 centers in the clinical trial. Subjects have been implanted an average of 6.9 (range of 1.2 – 8.6). The Argus II remains implanted and functioning in 24 subjects. The safety profile remains acceptable with most of the serious adverse events occurring within one year of implantation. Performance has remained better with the System ON than OFF on most visual tests. With 207 cumulative subject-years of clinical trial follow-up on 30 clinical trial subjects, this is the largest and longest study of a visual prosthesis to date. The results confirm previous reports on the ability of the Argus II prosthesis to provide visual function and functional vision over several years of chronic device use. These subjects will continue to be followed up on the test parameters reported herein.

4-4:20pm
**Animal studies of subretinal approach to prosthetic restoration of sight**
*Daniel Palanker, Hansen Experimental Physics Laboratory, Stanford University*

Subretinal prosthetic restoration of sight is based on introduction of the visual information by electrical stimulation of the non-spiking inner retinal neurons, and hence it has the potential to preserve many features of the retinal signal processing, unlike the direct stimulation of the ganglion cells in epiretinal approach. I will review the current status of the animal studies of prosthetic vision with subretinal implants based on electrophysiological (VEP) and behavioral measurements, and will illustrate preservation of the flicker fusion at high (>20Hz) frequencies, adaptation to static images, ON and OFF responses to slower (~2Hz) changes in the visual scene, and contrast sensitivity of about 12%. Grating visual acuity matched the pixel pitch of 65um, indicating that smaller pixels might further improve spatial resolution.

4:20-4:25pm - Questions
4:20-4:30pm - Summary and closing remarks
*Mark Pennesi, MD, PhD, Casey Eye Institute, Oregon Health & Science University*