324 Corneal dystrophies: Where do we stand? - Minisymposium
Tuesday, May 09, 2017 11:00 AM–12:45 PM
Ballroom 2 Minisymposium
Program #/Board # Range: 2934–2939
Organizing Section: Cornea

Program Number: 2934
Presentation Time: 11:03 AM–11:20 AM
Pathogenesis of granular corneal dystrophy type 2
Eung Kweon Kim. Ophthalmology, Yonsei University College of Medicine, Seoul, Korea (the Republic of).
Presentation Description: Granular corneal dystrophy type 2 (GCD2) is an autosomal dominant disorder caused by a point mutation in transforming growth factor-β induced gene (*TGFBI*). Accumulation of transforming growth factor beta-induced protein (TGFBIp) is involved in the pathogenesis of TGFBI corneal dystrophies; however, the exact molecular mechanisms are not fully elucidated. In GCD2 corneal fibroblasts, alterations of morphological characteristics of corneal fibroblasts,
increased susceptibility to intracellular oxidative stress, dysfunctional mitochondria, and cell cycle alteration were observed. Recently, delay of the autophagic clearance of mutant-TGFBIp is observed in GCD2 corneal fibroblasts. Future research should be directed toward elucidation of the biochemical mechanism of deposit formation, the relationship between the mutated TGFBIp and the other materials in the extracellular matrix, and the development of gene therapy including gene editing and drugs including agent for decrease of TGFBIp production.
Commercial Relationships: Eung Kweon Kim,
Avellino Lab USA (C)
Support: Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI) HI16C1009

Program Number: 2935
Presentation Time: 11:20 AM–11:37 AM
The role of decorin in the development of congenital stromal corneal dystrophy
Eyvind Rodahl[2, 1]. [1]Department of Ophthalmology, Haukeland University Hospital, Bergen, Norway; [2]Department of Clinical Medicine, University of Bergen, Bergen, Norway.
Presentation Description: Congenital stromal corneal dystrophy (CSCD) is a rare autosomal dominant disorder associated with mutations in the decorin gene (*DCN*). In patients, small stromal opacities are seen shortly after birth. Electron microscopy of CSCD corneas show disorganized collagen fibrils and areas of amorphous substance interspersed with normal stromal morphology. All mutations described so far are located in the last exon of *DCN*, and all result in a 33 amino acid truncation of decorin. After describing the first mutation in *DCN*, we have over the past years examined the consequences of the mutation. Truncated decorin aggregates more easily than normal decorin, and decorin accumulates in the stromal amorphous areas. We have therefore postulated that the corneal opacities arise mainly because decorin aggregates and is deposited in the corneal stroma. Recent morphological studies have revealed that the loss of the C-terminal end of decorin results in impaired binding of decorin to collagen. This leads to the generation of fibrils with varying diameter, and to loss of the regularity in normal collagen fibril morphology. We have also attempted to replicate CSCD in mice by establishing a knock-in mouse strain, 952delT *Dcn.* Mice were constructed by targeted mutation. Although the knock-in mice expressed a truncated form of decorin, the mice had clear corneas and normal corneal morphology. In contrast to truncated human decorin which is exported extracellularly, truncated mouse decorin was retained intracellularly in the endoplasmic reticulum. This could explain why the mouse corneas remained clear. The consequences of the decorin mutation are different in mice and humans, and the 952delT *Dcn* knock-in mouse is therefore not a suitable model for CSCD.
Commercial Relationships: Eyvind Rodahl, None
Support: Western Norway Regional Health Authority Grant 911746

Program Number: 2936
Presentation Time: 11:37 AM–11:54 AM
Keratoconus: An update on diagnosis and surgical treatments
Penny A. Asbell. Ophthalmology, Icahn School of Medicine at Mount Sinai, New York, NY.
Presentation Description: Keratoconus is the most common cause of non- inflammatory thinning of the cornea and is characterized by irregular astigmatism and loss of best corrected spectacle vision. Key issues in clinical care are: 1) providing good functional vision and 2) preventing progression. For the typical case, “you know it when you see it”, but more subtle cases are not so easily diagnosed. As new treatments become available, early diagnosis and then intervention becomes more critical. New approaches to diagnosis that go beyond corneal shape analysis, such as epithelial thickness, and biomechanics measurements are under exploration, but not as yet part of routine patient care. Defining progression at first glance seems obvious, but repeatable measurements of an abnormal cornea can be challenging and which metric is most indicative of progression is not clear. Despite these uncertainties, treatment options have expanded with newer contact lenses, intrastromal corneal inserts, cross-linking, endothelial preserving transplants (deep anterior lamellar keratoplasty, big bubble keratoplasty) and excimer refractive treatments – each considered alone and/or in combination. Such a large array of approaches in a disease that varies considerably, even between the 2 eyes of one patient, makes clinical trial design challenging but worth the effort given the effect of keratoconus on quality of life on patients who typically present as teenagers or in their twenties.
Commercial Relationships: Penny A. Asbell, None

Program Number: 2937
Presentation Time: 11:54 AM–12:11 PM
Insights into the molecular mechanisms of keratoconus
Dimitrios Karamichos. Ophthalmology, OUHSC, University of Oklahoma Health Sciences Center, Oklahoma City, OK.
Presentation Description: The common corneal dystrophy, Keratoconus, is associated with significant thinning of the central cornea leading to severe visual defects with onset usually post-puberty and stabilization by the fourth to fifth decade of life. Despite years of research, the pathophysiology of the disease remains elusive. This talk will discuss recent developments and updates on the molecular mechanisms of keratoconus.
Commercial Relationships: Dimitrios Karamichos, None
Support: EY023568

Program Number: 2938
Presentation Time: 12:11 PM–12:28 PM
Fuchs dystrophy: Genetics, gene expression and pathways
Keith Baratz. Ophthalmology, Mayo Clinic, Rochester, MN.
Presentation Description: Fuchs endothelial corneal dystrophy (FECD) is a common, inherited condition of the corneal endothelium and the most common indication for corneal transplantation in the U.S. Recent research has implicated a variety of genetic defects and biochemical alterations in the pathogenesis of disease, but effective alternatives to surgical treatment are unavailable. A majority of

U.S. cases of FECD have been linked to expansion of an intronic CTG trinucleotide repeat in the transcription factor 4 (*TCF4*) gene, and other genetic associations include *SLC4A11, ZEB1* and others. Oxidative stress, the unfolded protein response and alterations in extracellular matrix may play roles in the biology of the disease. The link between the genetic associations and biochemical changes remains unclear. The root cause of *TCF4*-associated disease may be RNA toxicity in which transcribed $(CUG)_n$ RNA sequesters critical splicing factors of the muscleblind family. The resulting widespread alterations in RNA splicing have been demonstrated by RNA sequencing technology. This pathogenic mechanism parallels that of myotonic dystrophy, type I, a neuromuscular degeneration due to CTG repeat expansion in the *DMPK* gene. The mechanisms leading to phenotypically identical FECD in cases due to genetic variants other than trinucleotide expansion and the specific pathways leading from RNA toxicity to oxidative damage, the unfolded protein response or other abnormalities are unknown. Despite the many gaps in knowledge regarding FECD biology, the implicated genetic and biochemical alterations allow speculation regarding medical therapy and prevention. This presentation will summarize the current data on associated genetic variants, implicated pathways and the status of disease models of FECD. We will discuss data supporting the CTG expansion and RNA toxicity as causative factors in FECD pathogenesis, review recent RNASeq data on gene mis-splicing and speculate on potential therapeutic targets.

Commercial Relationships: Keith Baratz, None

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Program Number: 2939
Presentation Time: 12:28 PM–12:45 PM

Developing drug therapies for Fuchs and corneal endothelial dysfunction

David Eveleth. Trefoil Therapeutics, San Diego, CA.

Presentation Description: Fuchs and other corneal endothelial dystrophies are slowly progressive conditions for which the only treatment is transplantation. Therapies for these conditions need to address not only the underlying cell biology but the practical aspects of clinical development. Development of therapies that halt degeneration is very challenging, and because most patients present with advanced degeneration, a therapy that can regenerate the endothelium is needed. The endogenous stimulator of endothelial growth, FGF, is impractical to use due to delivery and pharmacokinetic/pharmacodynamic problems. Engineered versions of FGF-1 that have improved pharmacological properties have been found to stimulate regeneration of endothelial cells in vitro, in organ culture and in vivo using animal models. The regenerated cells have a normal morphology and density. Clinical demonstration of efficacy will require not only the demonstration of the cell biological endpoints but impacts relevant to the patient such as resolution of bullous keratopathy. Challenges for the development of drug therapies for Fuchs will be discussed.

Commercial Relationships: David Eveleth, Trefoil Therapeutics (E)