STATE BOARD OF OPTOMETRY
2450 DEL PASO ROAD, SUITE 105, SACRAMENTO, CA 95834
P (916) 575-7170 F (916) 575-7292 www.optometry .ca.gov

Continuing Education Course Approval Checklist

Title: Rock Inhibitors and Cornea

Provider Name: Kaiser Permanente c/o Dr. Wendy Friedman

☑Completed Application
Open to all Optometrists? ☑Yes ☐No
Maintain Record Agreement? ☑Yes ☐No

☑Correct Application Fee

☑Detailed Course Summary

☑Detailed Course Outline

☑PowerPoint and/or other Presentation Materials

☐Advertising (optional)

☑CV for EACH Course Instructor

☑License Verification for Each Course Instructor
Disciplinary History? ☐Yes ☑No

OPTOMETRY

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CONTINUING EDUCATION COURSE APPROVAL APPLICATION

$50 Mandatory Fee

Pursuant to California Code of Regulations (CCR) § 1536, the Board will approve continuing education (CE) courses after receiving the applicable fee, the requested information below and it has been determined that the course meets criteria specified in CCR § 1536(g).

In addition to the information requested below, please attach a copy of the course schedule, a detailed course outline and presentation materials (e.g., PowerPoint presentation). Applications must be submitted 45 days prior to the course presentation date.

Please type or print clearly.

Course Title	**Course Presentation Date**
ROCK Inhibitors and Cornea	09/17/2016

Course Provider Contact Information

Provider Name

Wendy (First) Friedman (Last) _____ (Middle)

Provider Mailing Address

Street 393 East Walnut St **City** Pasadena **State** CA **Zip** 91188

Provider Email Address Wendy.L.Friedman@kp.org

Will the proposed course be open to all California licensed optometrists?	☒ YES ☐ NO
Do you agree to maintain and furnish to the Board and/or attending licensee such records of course content and attendance as the Board requires, for a period of at least three years from the date of course presentation?	☒ YES ☐ NO

Course Instructor Information

Please provide the information below and attach the curriculum vitae for each instructor or lecturer involved in the course. If there are more instructors in the course, please provide the requested information on a separate sheet of paper.

Instructor Name

Natalie (First) Afshari, MD (Last) _____ (Middle)

License Number _____	**License Type** _____
Phone Number (858) 534-6290	**Email Address** drafshari@ucsd.edu

I declare under penalty of perjury under the laws of the State of California that all the information submitted on this form and on any accompanying attachments submitted is true and correct.

Signature of Course Provider *Date* 1/9/17

KAISER PERMANENTE®

Southern California Permanente Medical Group
Professional Education
393 East Walnut
Pasadena, California 91188
(626) 405-4644

November 21, 2016

Dear California Board of Optometry,

This letter is to correct the missing application pieces for the 2016 Ophthalmology Symposium at the Disneyland Hotel on Saturday, September 17, 2016

Enclosed is

- a check for $300.00
- a detailed summary of each course
- outlines for each course
- powerpoint slides – which can also be viewed on the website (link below)

The reason the application was late

The delay was due to not knowing the status of one of our speakers (Nadia Waheed, MD) so the agenda wasn't finalized.
She was originally scheduled to speak twice in the morning but then she informed us she was asked to present at a different symposium on the same day in San Diego. We didn't know until very close to the symposium if she would have to cancel or would be able to switch to an afternoon slot or she would only speak once and have another colleague take her other slot. What was finally settled upon is she would switch to the afternoon slot and give the other slot away to her colleague.

Your letter requested a CV for Dr. Garrick Chak.

He was the chair of the committee and introduced the day and all the speakers – he didn't give any presentation.

Below is the link to our registration website that has more information and shows that Southern California Permanente Medical Group (accredited by the Institute for Medical Quality/California Medical Association (IMQ/CMA) to provide continuing medical education for physicians – and they have approved this symposium for ***6.5 AMA PRA Category 1 Credit(s)™***
https://www.signup4.net/public/ap.aspx?EID=PHYE530E&OID=50

I can email you soft copies (if you prefer) or if you need any more information, please feel free to contact me.

Sincerely,

Wendy Friedman
Meeting Planner
393 East Walnut, Pasadena, CA 91188 626) 405-4644 wendy.L.friedman@kp.org

10:30 am -11:15 am
ROCK Inhibitors and Cornea
SPEAKER: Natalie Afshari, MD

DETAILED SUMMARY: The corneal endothelium is a single layer of cells that is vital for ocular transparency. ROCK inhibitors have been a recent research development that show promise for corneal endothelial regeneration. Evidence based guidance on the new developments with this pharmacotherapy may enhance quality of vision and potentially avoid the associated risks of surgery.

Overall, recent studies by the Institute of Medicine, RAND, and others have called attention to the gap between scientifically supported approaches to care and day-to-day practice by clinicians. Health plans and large employers have targeted the *gap between knowledge and practice as the root cause for inappropriate variability in practice patterns.*

SCPMG physicians need to be aware of and prepare for use of emerging technology and medications, the gap between knowledge and practice is significant, and physicians do not routinely adhere to evidence-based guidelines when known.

OBJECTIVES - At the end of this activity, participants should be able to:

- Examine the evidence for use of Rho Kinase (ROCK) Inhibitors to treat glaucoma and cornea; develop and implement a plan to integrate into practice

- Incorporate treatment recommendations for endothelial surgery and reduce variability of practice

TOPICAL OUTLINE

1. DLEK to DSEK to DMEK to Rock
    a. ROCK and Cornea
2. Fuchs Dystrophy
    a. Features
    b. ROCK Structure
    c. Pathogenesis
    d. Pathology
    e. Dystrophy
    f. Corneal Pachymetry
3. Implications

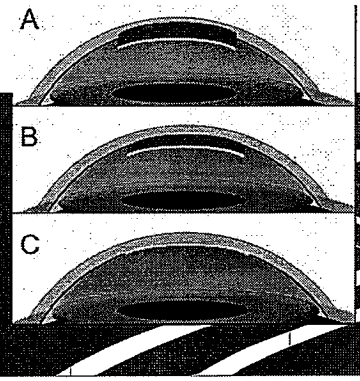
ROCK Inhibitors and Cornea

Natalie Afshari, MD FACS
Stuart I Brown MD Chair in Ophthalmology in Memory of Donald P Shiley
Professor of Ophthalmology
Chief of Cornea and Refractive Surgery
Vice Chair of Education
University of California San Diego

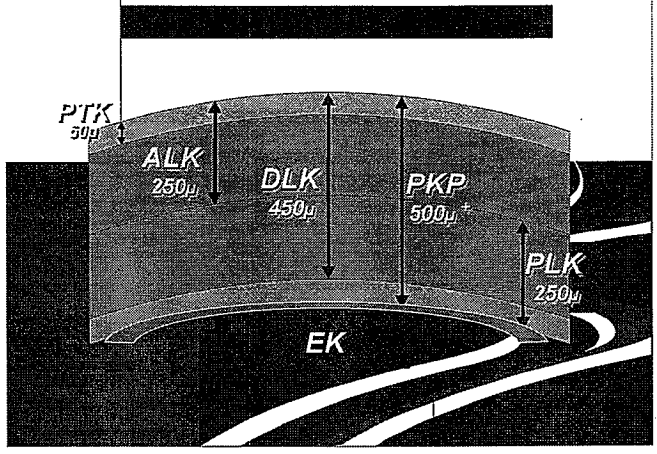
Financial Disclosure

- National Eye Institute
- Research To Prevent Blindness

DLEK TO DSEK to DMEK to ROCK

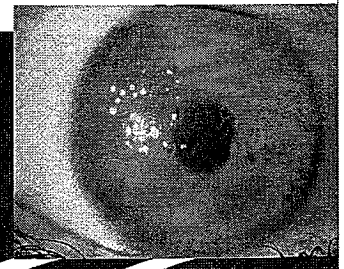


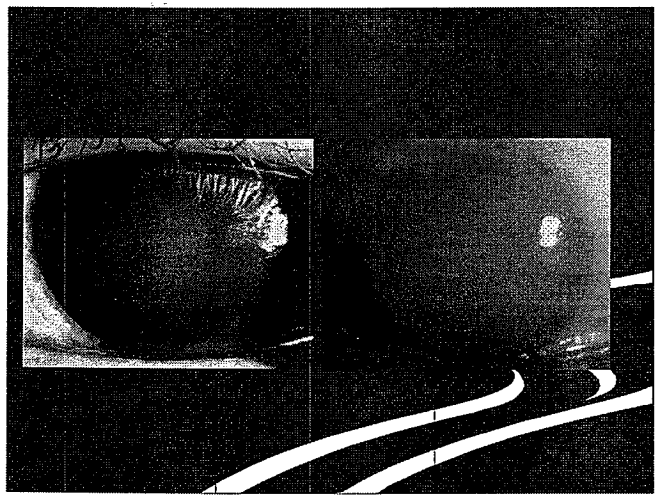
From DLEK to ~~DMEK~~



Fuchs Dystrophy

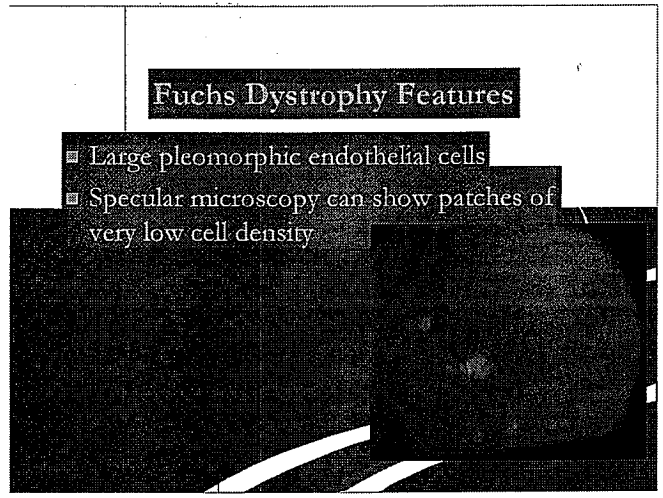
- Common corneal disorder
- Late age of onset
- Bilateral corneal endothelium dysfunction causes edema





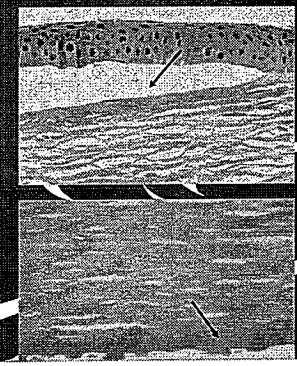
Fuchs Dystrophy Features

- Large pleomorphic endothelial cells
- Specular microscopy can show patches of very low cell density



Fuchs Dystrophy Pathology

- Thickened Descemet's with excrescences
- Attenuated endothelial cell layer
- Increased endothelial pigmentation



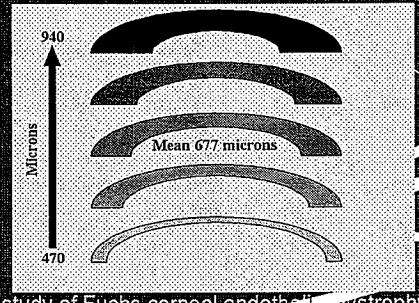
Fuchs Dystrophy

- One of the leading indications for penetrating keratoplasty

Kang PC, Klintworth GK, Carlson A, [illegible] T, Afshari N[illegible]

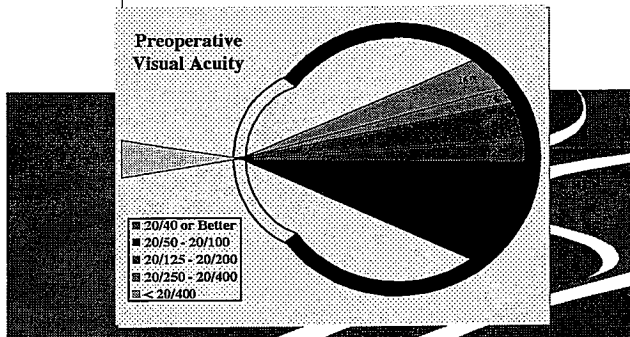
Trends in the indications for penetrating keratoplasty, 1980-[illegible]
Cornea 2005; 24:801-3

Corneal Pachymetry

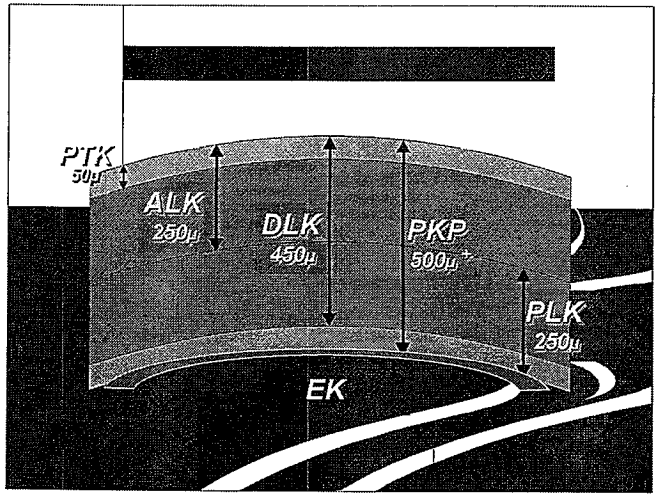


A clinical study of Fuchs corneal endothelial dystrophy over a thirty-year period (1972-2001)

Afshari, et al. *Arch Ophthalmol* 2006



Afshari, et al. Arch Ophthalmol 2006



Evolution of EK

- 1960s Dr. Barraquer
- EK using an anterior approach via corneal flap
  - Less donor tissue
  - Still a lot of sutures
  - Still get astigmatism and vascular ingrowth

PLK/DLEK

- Posterior Lamellar Keratoplasty
  - Dr. Gerrit Melles
  - Deep Lamellar EK (Dr. Mark Terry)
- Manual dissection of both donor and host stromal beds:
  - Though a large 5-9mm sclerocorneal wound, posterior lamella, DM, and endothelium dissected

DSEK

- Dissect only the DM from recipient eye
  - Dr. Gerrit Melles,
    - modified by Dr. Gorovoy and Dr. Price

DSAEK

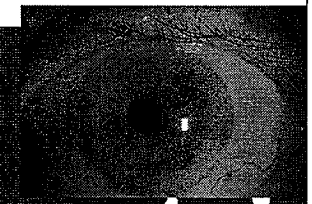
- To improve graft-host interface, donor cornea dissected with automated microkeratome.

DMEK

- Dr Gerrit Melles
  - stripped donor DM, inject into AC, unrolled with pneumatic and fluidic manipulations. Use the same air bubble technique.
  - No need for microkeratome (developing areas)
  - Less myopic shift, less immunologic graft reactions, less 2nd glaucoma from prolonged steroid use compared to DSEK

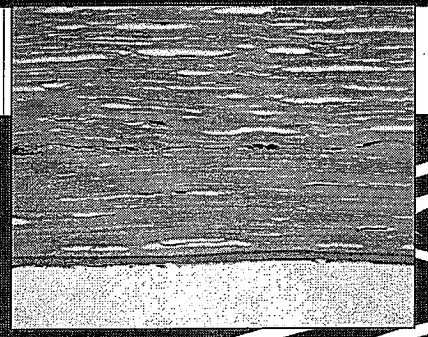
EK vs PK

- Faster visual rehabilitation
- More predictable refractive outcomes
- Decreased risk of rejection
- Retention of corneal structural integrity



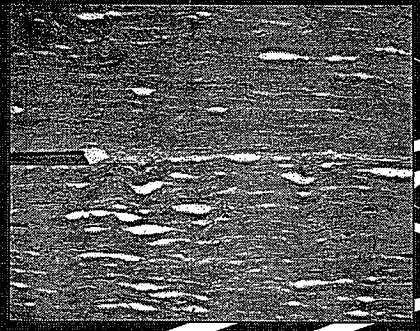
DMEK

Interface Pigment and Debris



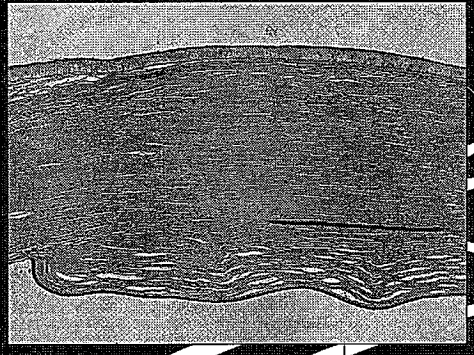
Caldwell M, Afshari NA, Decroos C, Proia A. Histology of DSEK graft adhesion. Am J Ophthalmol. 2009

Absence of Interface Scarring



Caldwell M, Afshari NA, Decroos C, Proia A. Histology of DSEK graft adhesion. Am J Ophthalmol. 2009

Interface Descemet's Membrane



Detached DSEK

DSEK Dislocation to Posterior Segment "Dropped DSEK"

- Eight Cases
- 5 sutured PCIOL
- 2 Aphakic
- All required repeat graft
- 6/8 required PPV
- VA 20/30 to LP

Dropped DSAEK: Dislocation of the Donor Graft to the Posterior Segment in Descemet's Stripping Automated Endothelial K[illegible]plasty

Natalie A Afshari [illegible] Am J Ophthalmol. [illegible]

Endothelial Injury in DSEK

A Simple Maxim

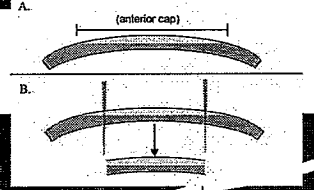
Corneal Endothelial Cells are Extremely Fragile

Along comes DSEK

Endothelial Cell Injury

1. Donor endothelial graft preparation
2. Insertion of donor graft through small incision
3. Graft tissue manipulation
4. Air tamponade of donor graft

Graft Preparation



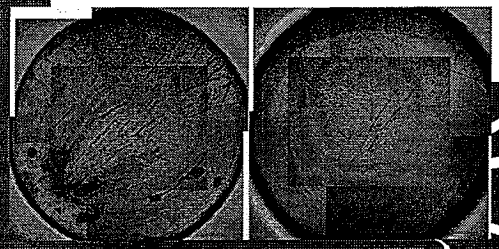
Graft Insertion

Kuo A, Harvey T, Afshari NA
Endothelial Graft Injury
Am J Ophthalmol 2008

Endothelial Cell Injury From Insertion & A Novel Delivery Technique

Kuo AN, Harvey T, Afshari NA.
Am J Ophthalmol. 2008

Forceps vs Cartridge



P<0.006

26% injury

9% injury

Kuo AN, Harvey T, Afshari NA.
Am J Ophthalmol. 2008

Air Bubble-Associated Endothelial Trauma in Descemet's Stripping Automated Endothelial Keratoplasty

Hong A, Caldwell M, Kuo A, Afshari NA.
Am J Ophthalmol 2009

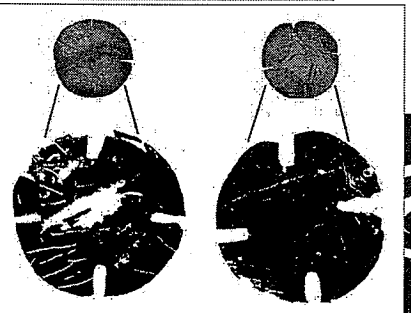
Post-op Day 1

Summary Data of the Proportion of Viable Endothelium (viable graft area divided by total countable graft area)

	Proportion of Viable Endothelium		
Pair	Air Bubble	Control	P Value
1	88.2 %	97.3 %	
2	85.3 %	98.4 %	
3	79.5 %	97.8 %	
4	72.5 %	91.1 %	
5	78.5 %	91.5 %	
6	80.0 %	91.9 %	
Mean ± SD	79.8 ± 0.04 %	89.9 ± 0.02 %	0.03

SD = Standard deviation
The mean difference in proportion of viable endothelium was 10.1% (more injury with air bubble trauma)

Paired human corneal endothelial lamellar grafts comparing injury due to air bubble trauma compared to control



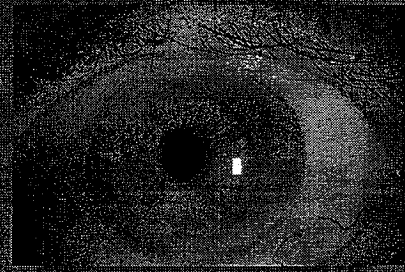
Air Bubble-traumatized Control

Hong A, Caldwell M, Kuo A, Afshari NA.
Am J Ophthalmol 2009

Post-Op Day 1

- 20/30 UCVA

Rethinking damage



- The "magic number" concept

DMET

- Descemet's Membrane Endothelial Transfer
- Upper edge of graft is fixated within the corneal tunnel incision to secure a contact area between graft and host posterior stroma.

Mechanism of Corneal Clearance

- Endothelial cell migration (both host and donor cells)

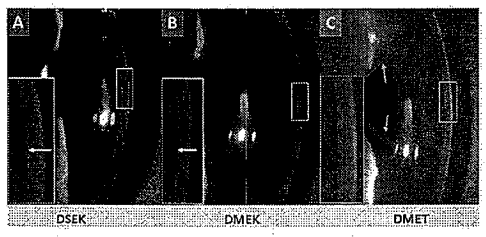


Fig. 1—Slit-lamp images of 3 eyes after A, DSEK; B, DMEK; and C, DMET surgery, at 6 months postoperatively. Note that a donor-to-host stromal interface is clearly visible in the DSEK (A, *white arrow*), but not the DMEK eye (B, *white arrow*). In the DMET eye (C), a free-floating Descemet graft is positioned inside the recipient anterior chamber (*orange arrows*), whereas in both the DSEK (A) and the DMEK (B) eye, the graft is positioned against the recipient posterior stroma. Note that all 3 recipient corneas show normal thickness and stromal clarity with functional endothelium.

DMET downsides

- Need wait 3-6 mo for clear cornea
- ECD at 6 mo (500-800 cells/mm) much less than EK.

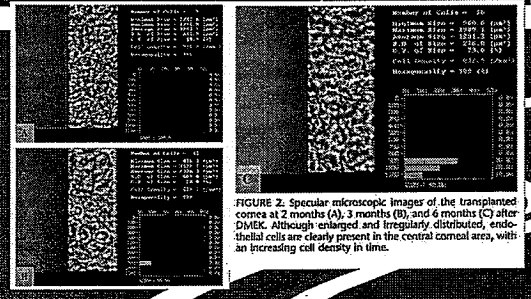
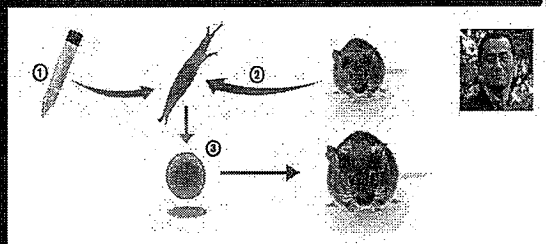


FIGURE 2. Specular microscopic images of the transplanted cornea at 2 months (A), 3 months (B), and 6 months (C) after DMEK. Although enlarged and irregularly distributed, endothelial cells are clearly present in the central corneal area, with an increasing cell density in time.

Future Direction

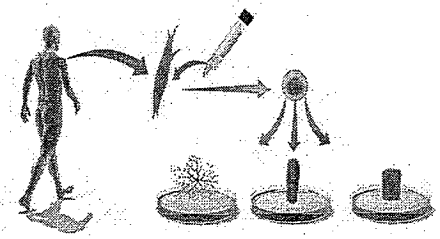
Nobel Prize 2012: Shinya Yamanaka

- Transferring 4 genes results in induced pleuripotent stem cells (iPS)



Nobel Prize 2012

- Induced pleuripotent stem cells (iPS) can now be generated from humans

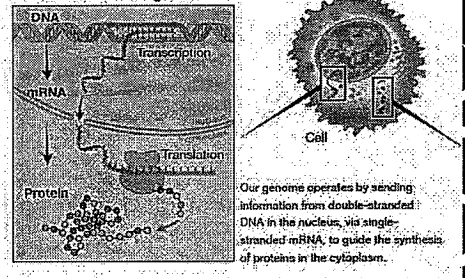


Interfering RNA

RNA interference

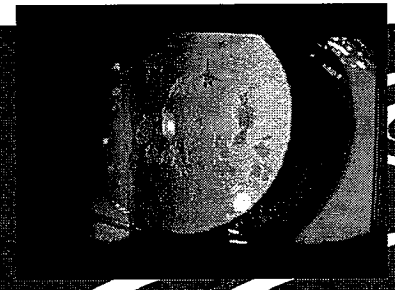
— gene silencing by double-stranded RNA

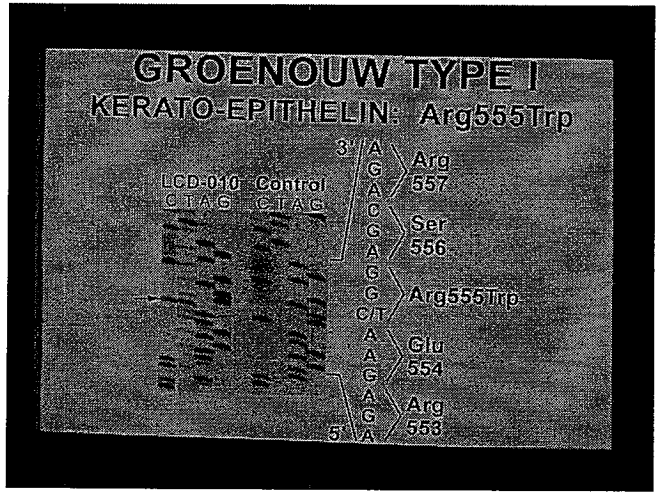
1. The central dogma

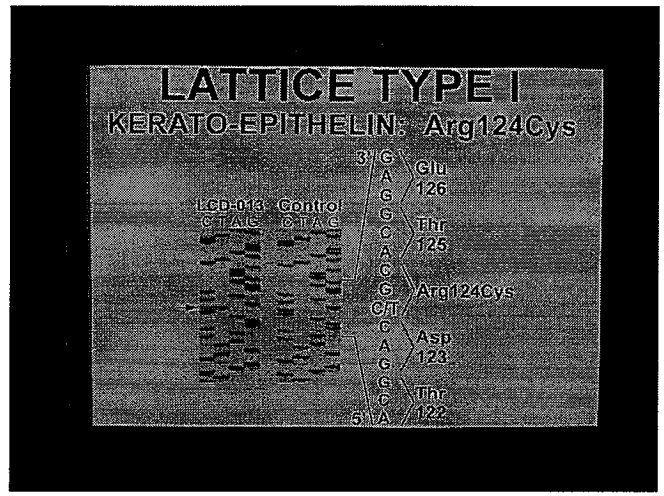


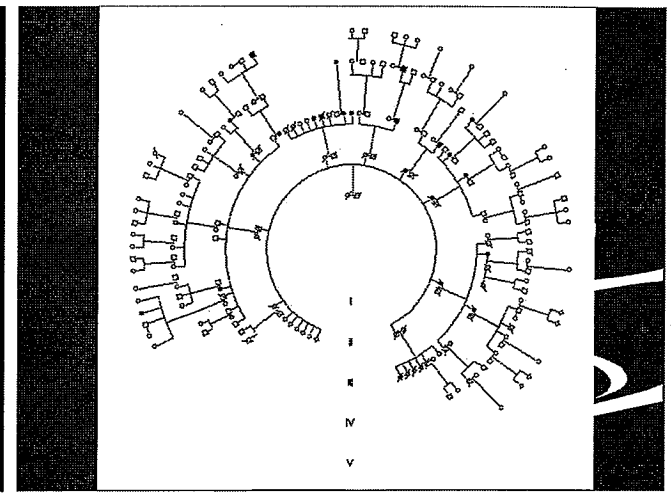
Our genome operates by sending information from double-stranded DNA in the nucleus, via single-stranded mRNA, to guide the synthesis of proteins in the cytoplasm.

Corneal Dystrophies & The Promise of Gene Therapy in Cornea









1st GWAS
Baratz, et al NEJM 2010

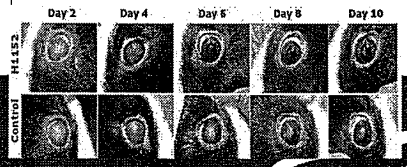
- 130 unrelated cases
- 260 unaffected controls
- Illumina 370K beadChip panel
- Replication set of 150/150
- SNP on chromosome 18q21, rs613872 in an intron of a gene encoding transcription factor 4 (TCF4) showed genome-wide significant association with Fuchs

Fuchs Genetics Consortium

- A genome wide association study grant from Center for Inherited Diseases
- Over 2000 DNA samples between Fuchs cases and controls
- 2.5 million array of Illumina
- Genotyping results will be out in April
- Followed by Analysis

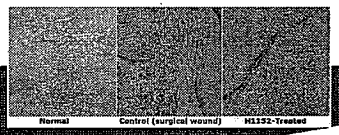
ROCK Topical Therapy?

ROCK Therapy and Corneal Endothelium



Rabbit *In vivo* corneal wound healing with topical administration of H1152. Compared to control (BSS), topical administration of 1 μM H1152 3-4 times daily for 10 days led to faster and more complete resolution of corneal edema associated with surgical debridement of the corneal endothelium. Rabbit eyes were examined daily using photography, slit lamp examination, and handheld ultrasound pachymetry.

ROCK and Endothelium



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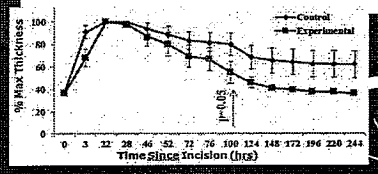
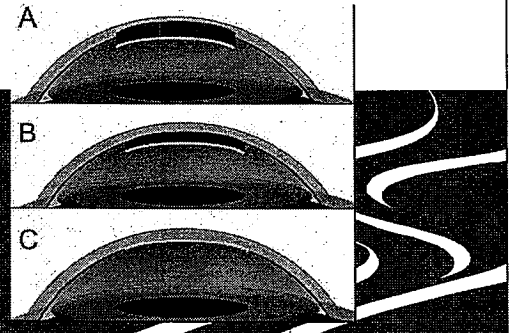
ROCK and Pachymetry



Effect of H1152 on corneal thickness *In vivo*. Corneal thickness measurements were recorded daily for each rabbit, averaged and normalized as a percentage of maximum recorded thickness for each rabbit. H1152-treated eyes showed more resolution (faster thinning) than BSS.

DLEK TO DSEK to DMEK to ROCK



Thank You!

ROCK Inhibitors and Cornea
Natalie Afshari, MD FACS
Stuart I Brown MD Chair in Ophthalmology in Memory of Donald P Shiley
Professor of Ophthalmology
Chief of Cornea and Refractive Surgery
Vice Chair of Education
University of California San Diego
Financial Disclosure

- National Eye Institute
- Research To Prevent Blindness

DLEK TO DSEK to DMEK to ROCK
From DLEK to ~~DMEK~~

ROCK and Cornea

- inhibition of Rho-associated kinase (ROCK) has been reported to have a stimulatory effect on corneal endothelial wound healing, a finding with significant implications for treating CED (Koizumi et al., 2012)

ROCK and Cornea

- Inhibition of the ROCK signaling pathway with ROCK inhibitor Y-27632 resulted in inhibition of apoptosis and increased proliferation of corneal endothelial cells (CECs) isolated from the cynomolgus monkey (Okumura et al., 2009).
- Topical administration of ROCK inhibitor Y-27632 augmented cell proliferation *in vitro* and *in vivo* (Okumura et al., 2011).

Fuchs Dystrophy Features

- Large pleomorphic endothelial cells
- Specular microscopy can show patches of very low cell density

ROCK Structure

- ROCK is a widely-studied serine/threonine kinase that functions as an effector molecule of the RhoA signaling pathway with important roles in regulating cell morphology, motility, and polarity via its rearranging effects on the actomyosin cytoskeleton. Specifically, activation of ROCK leads to formation of actin stress fibers, increased cell-cell junctions, as well as increased cell-extracellular matrix interactions (Feng et al., 2015; Rao and Epstein, 2007)

Fuchs Dystrophy

- Common corneal disorder
- Late age of onset
- Bilateral corneal endothelium dysfunction causes edema

Fuchs Dystrophy Features

- Large pleomorphic endothelial cells
- Specular microscopy can show patches of very low cell density

Fuchs Pathogenesis

- Unclear
- Endothelial cells do not divide
  - Arrested in G1 phase of the cell cycle
  - Decrease with age
- Cells regulate the fluid status by Na+-K+ ATPase pumps

Fuchs Dystrophy Pathology

- Thickened Descemet's with excrescences
- Attenuated endothelial cell layer
- Increased endothelial pigmentation

Fuchs Dystrophy

- One of the leading indications for penetrating keratoplasty

Kang PC, Klintworth GK, Carlson A, Kim T, Afshari NA.

Trends in the indications for penetrating keratoplasty, 1980-2001. Cornea 2005; 24:801-3

Corneal Pachymetry

Implications of ROCK Inhibitors in Treatment of Fuchs Dystorphy

Video

Thank You!

Dr. Afshari is Stuart Brown MD Chair in Ophthalmology in Memory of Donald P. Shiley, Chief of Cornea and Refractive Surgery, Director of Education, and Professor of Ophthalmology at the Shiley Eye Institute, University of California San Diego. Prior to this, she was Professor of Ophthalmology and Director of Centers of Excellence at the Duke University Eye Center. She received her medical degree from Stanford University and her residency and fellowship training at Harvard University, Massachusetts Eye and Ear Infirmary. Dr. Afshari is the recipient of the Senior Achievement Award and the Secretariat Award by the American Academy of Ophthalmology and has been named a Gold Fellow of the Association for Research in Vision and Ophthalmology. She has received the inaugural Top Ten Women in Medicine award by Triangle News, Women Who Mean Business award by San Diego Business Journal, and the Teacher of the Year award from the Duke University Eye Center. She has also been recognized in the Best Doctors in America in each listing for the past decade, and was named in the U.S. News & World Report's Top Doctors List. Dr. Afshari is the co-editor of a new two-volume cornea book called "Principles and Practice of Cornea". She is also on the editorial board of American Journal of Ophthalmology, and Investigative Ophthalmology and Visual Science. She has previously served on the EyeNet editorial board, BCSC Cornea text book committee, and the American Academy of Ophthalmology council representing the American Society of Cataract and Refractive Surgery. She was co-chair of the cornea program committee for the Association for Research in Vision and Ophthalmology and co-director of Cornea Subspecialty Day for the American Academy of Ophthalmology. She is currently the chair of the American Society of Cataract and Refractive Surgery FDA Committee. Her NIH research grant is on the study of Fuchs dystrophy, and she investigates the intricacies of endothelial keratoplasty and regeneration of cornea.