Optometric Education Consultants

The Non-Healing Cornea
Neurotrophic Keratitis

Greg Caldwell, OD, FAAO

Mid-Winter Getaway
Optometric Education Consultants

Sunday, January 28, 2024

Disclosures- Greg Caldwell, OD, FAAO

All relevant relationships have been mitigated

- Lectured for: Alcon, B&L, BioTissue, Dompé
  - Disclosure: Receive speaker honorariums
- Advisory Board: Dompé, ImmunoGen, Iveric
  - Disclosure: Receive participant honorariums
- I have no direct financial or proprietary interest in any companies, products or services mentioned in this presentation
  - Disclosure: Non-salaried financial affiliation with Pharmanex
- Healthcare Registries – Chairman of Advisory Council for Diabetes and AMD
- The content of this activity was prepared independently by me - Dr. Caldwell
- The content and format of this course is presented without commercial bias and does not claim superiority of any commercial product or service
- Optometric Education Consultants – Scottsdale, AZ, Pittsburgh, PA, Sarasota, FL , Barcelona, Spain, Orlando, FL, Mackinac Island, MI, Quebec City, Canada, and Nashville, TN- Owner

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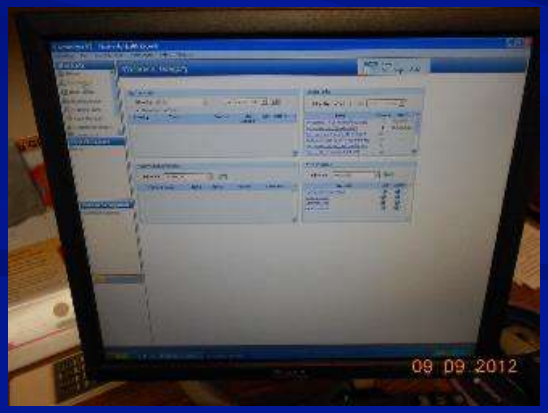
My Practice

I am a clinician first then a scientist

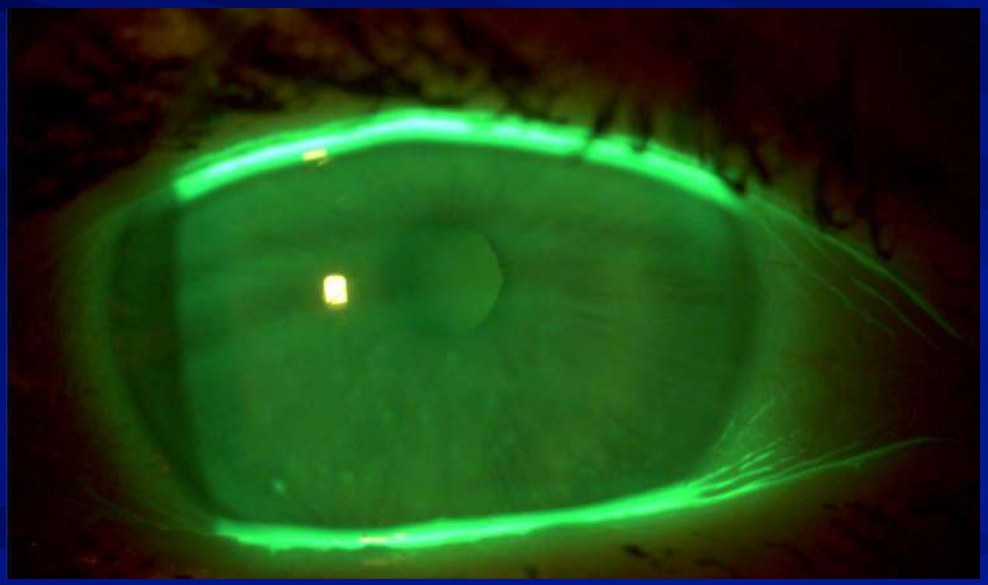
- Some are scientists first then clinician
- I need to simplify for patient and patient care.
- Science is great, but not good if there isn't a clinical application.
- Some lectures are science based without clinical application.
- My lecture will be a hybrid. Showing clinical applications of the science

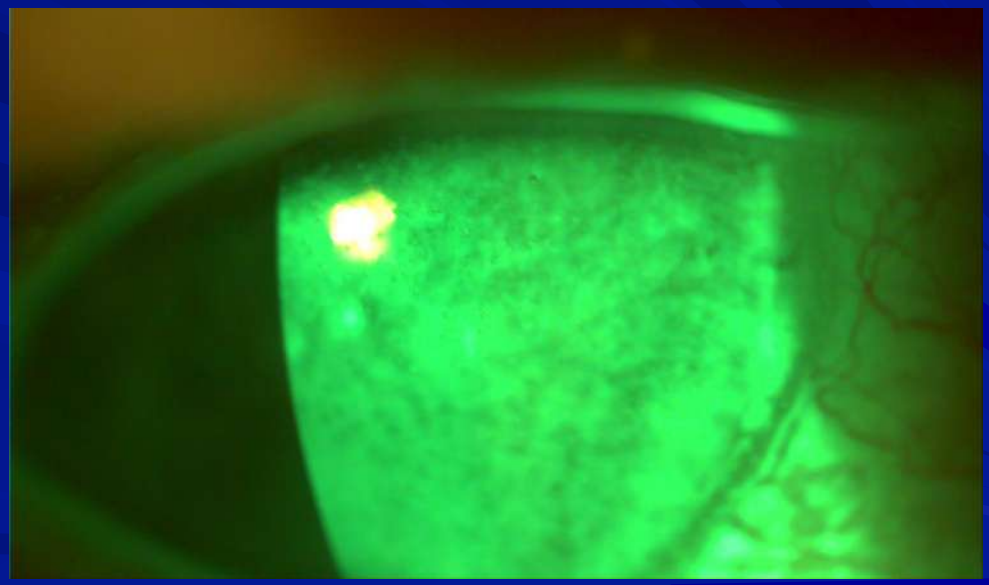


It is wonderful to have someone who's juggling so many aspects of optometry [scientific, clinical experience, teacher & lecturer]. It is refreshing and very informative. -Sarah

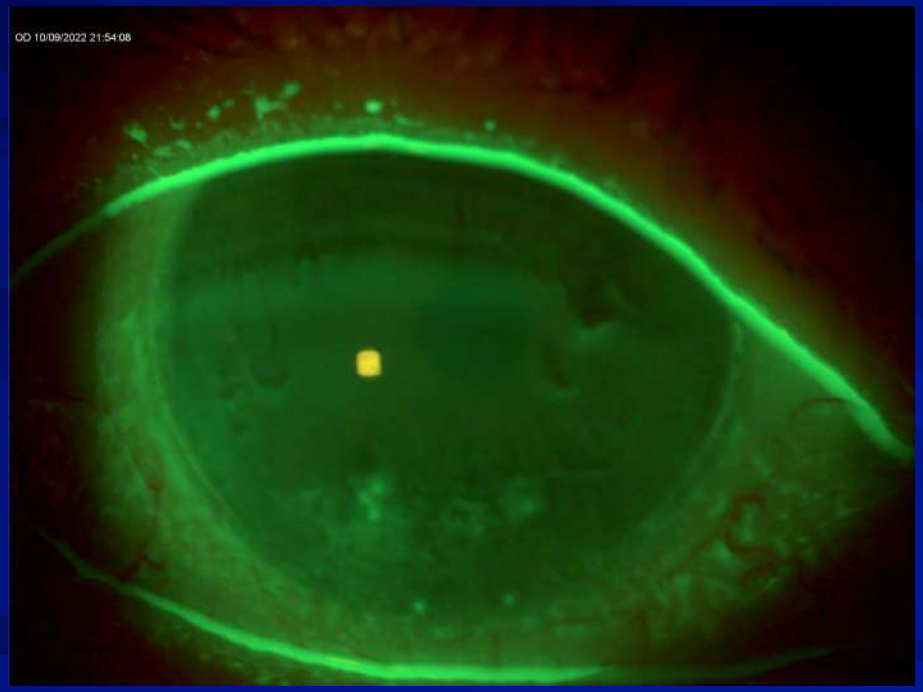
Which Eye is More Symptomatic?

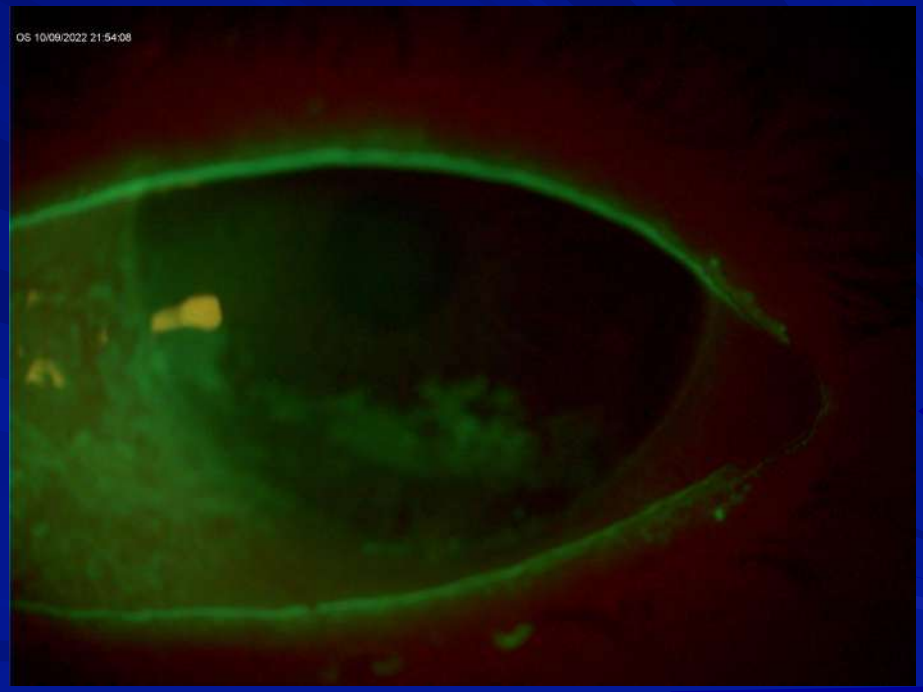
Stain without pain!



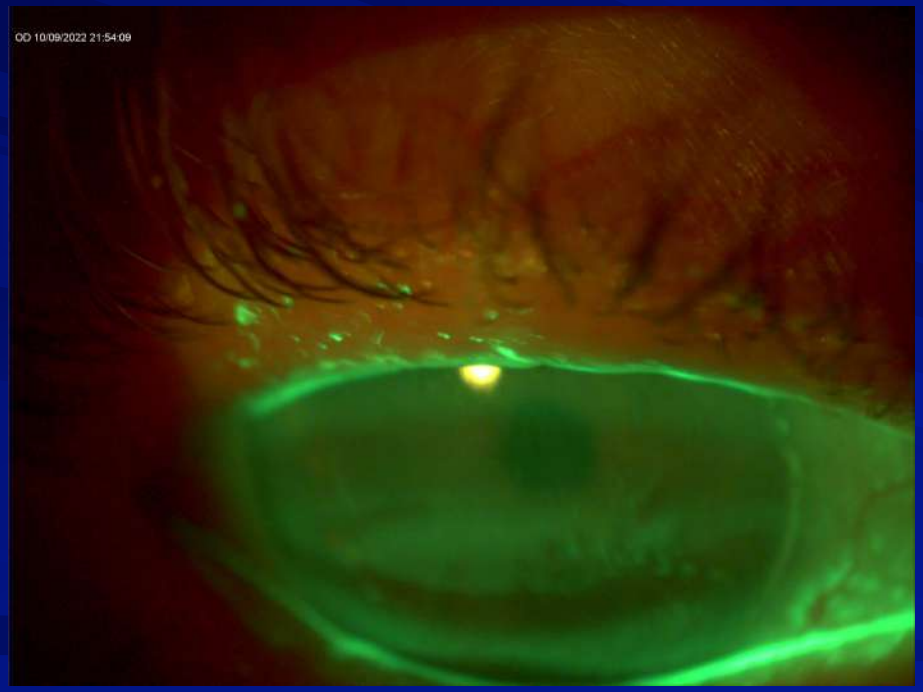


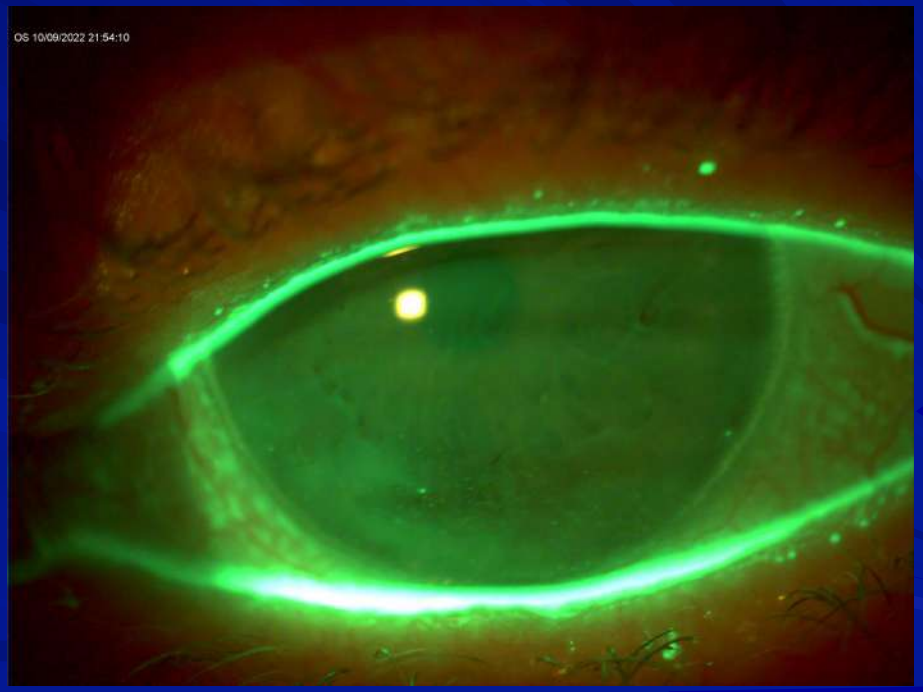
Before Oxervate™ (cenegermin-bkbj) Treatment





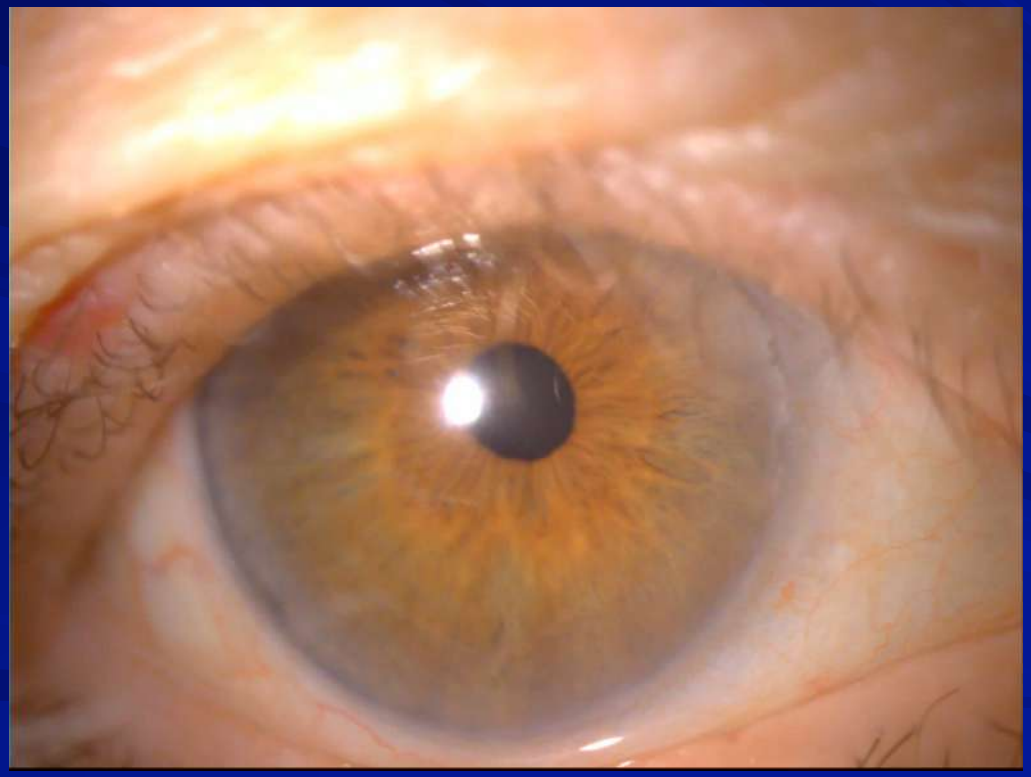
After Oxervate™ (cenegermin-bkbj) Treatment



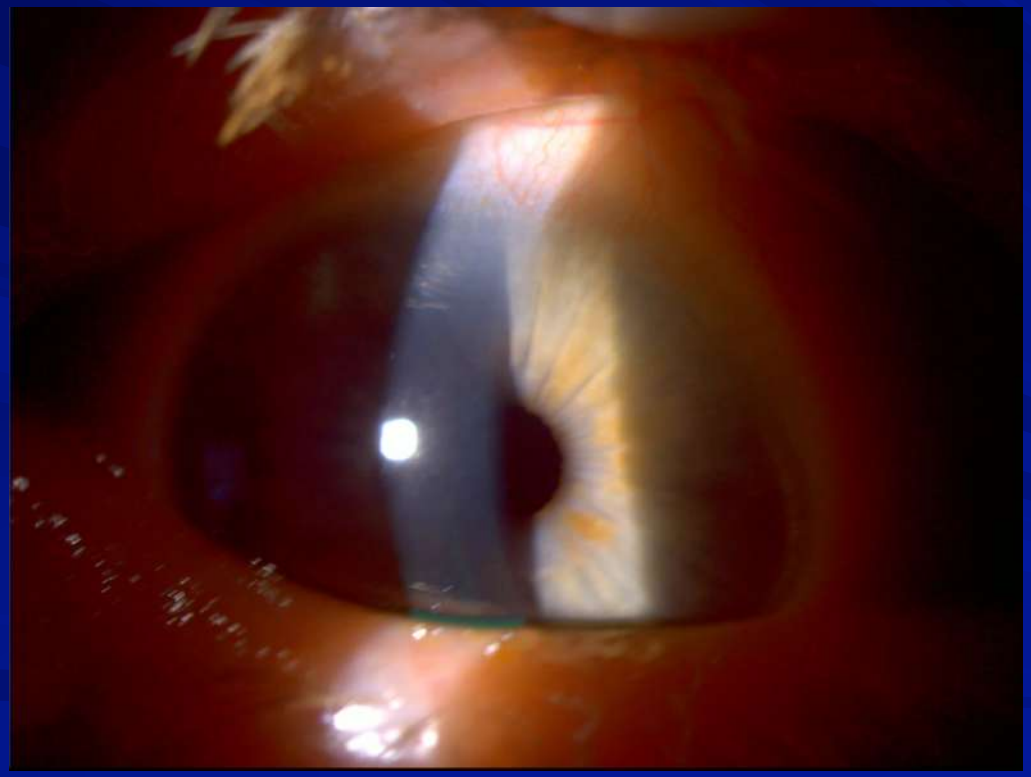


Corneal Sensitivity Testing

Cornea Sensitive Testing – Another Patient



Cornea Sensitive Testing – Yet Another Patient

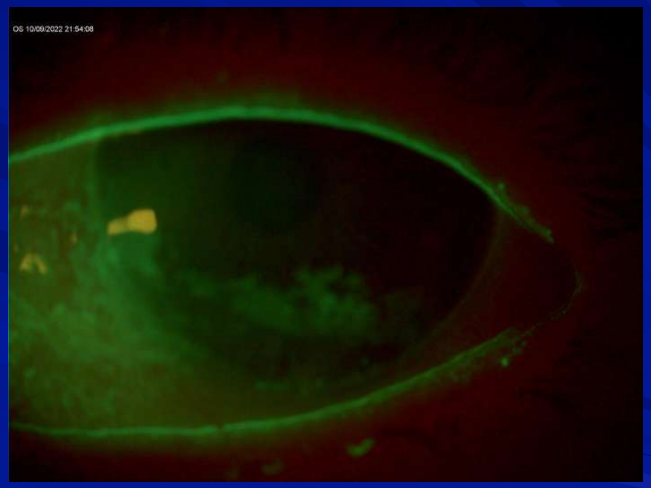


Oxervate™ (cenegermin-bkbj)

- Grading corneal sensitivity: (Cotton Tip)
  - Normal
  - Reduced
  - Absent

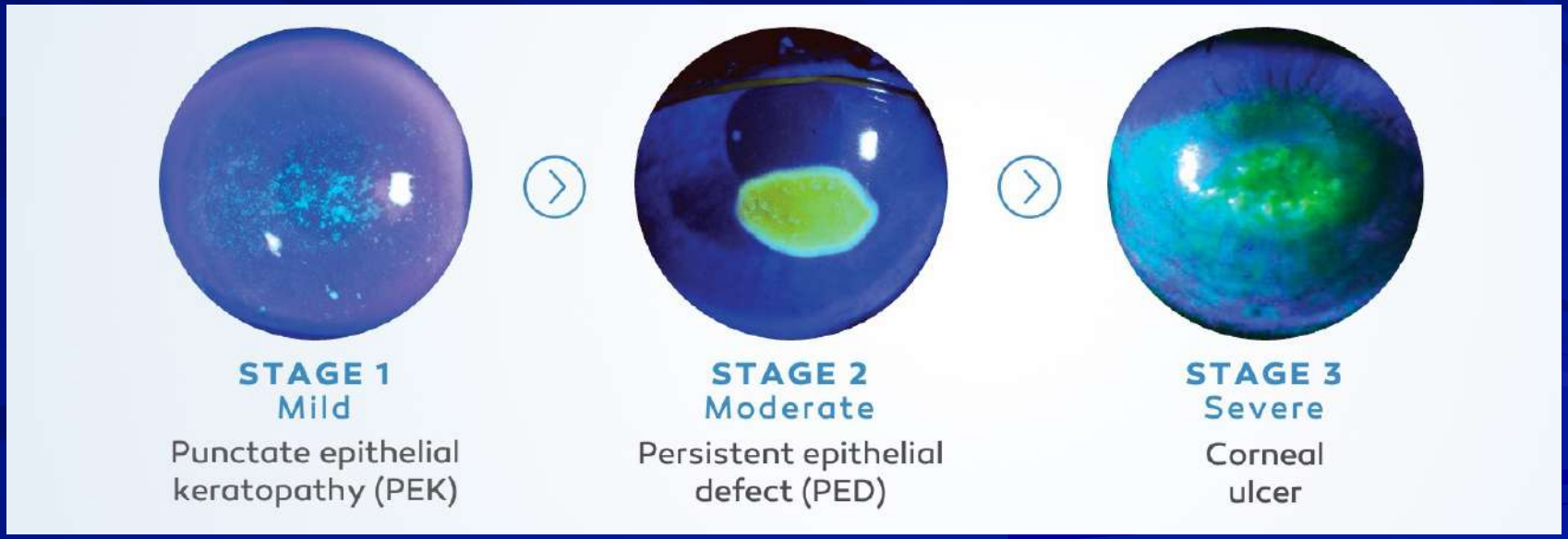
  - Reduced in all quadrants and centrally
  - Absent inferior quadrant, reduced everywhere else

- Neurotrophic Keratitis: (Staining)
  - Mild – Stage 1
  - Moderate – Stage 2
  - Severe – Stage 3



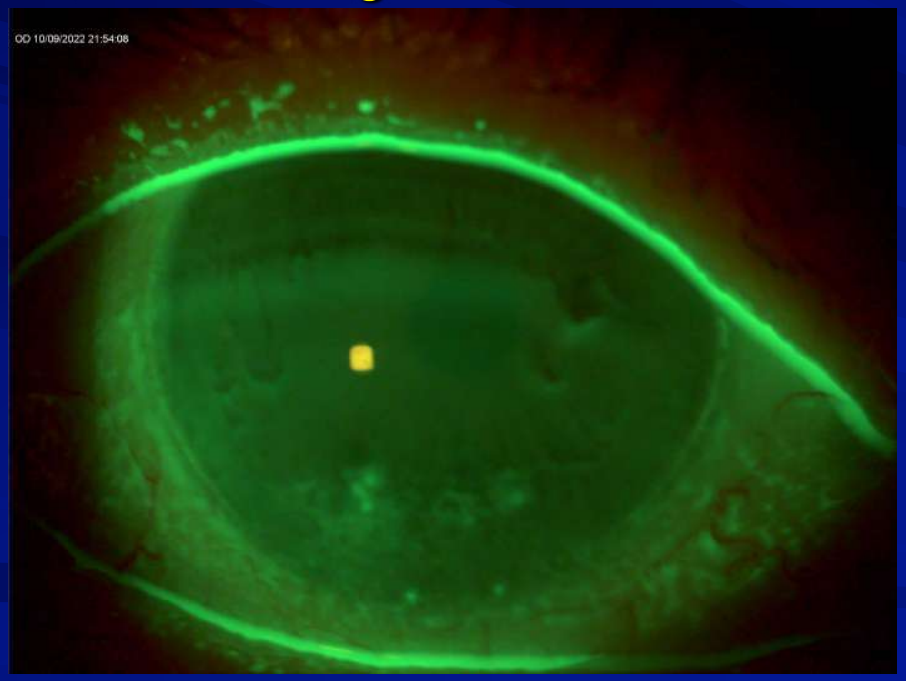
Neurotrophic Keratitis is a Degenerative Disease

- The Mackie classification represents one way to assess or grade NK – stage or progression

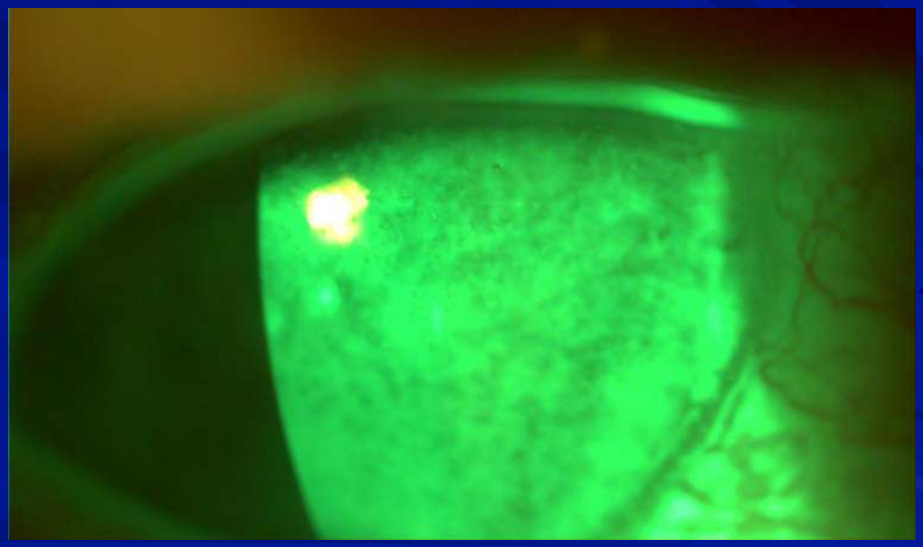


Mackie Classification

Moderate - Stage 2

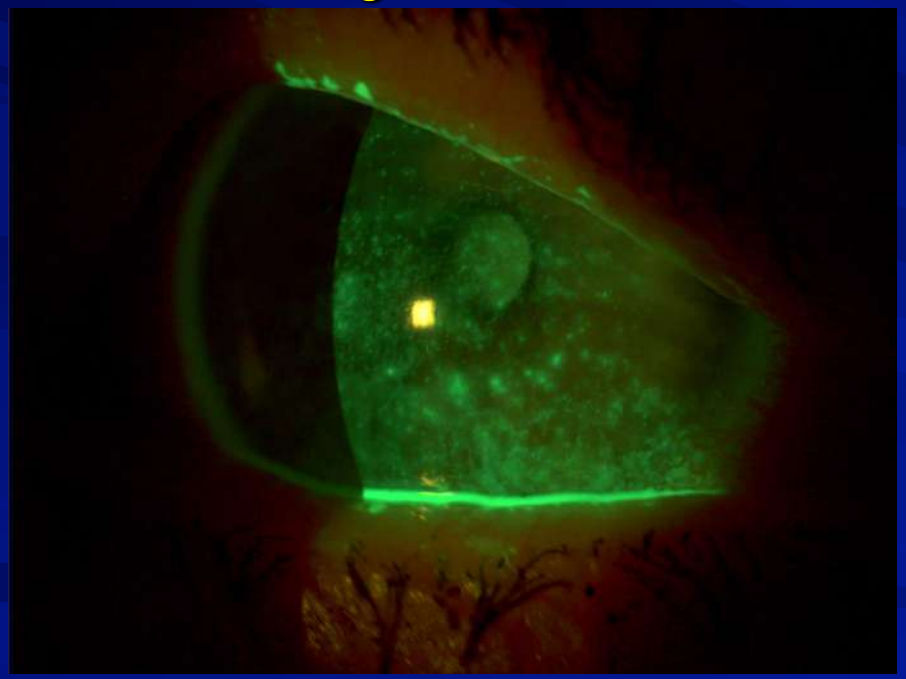


Moderate - Stage 2

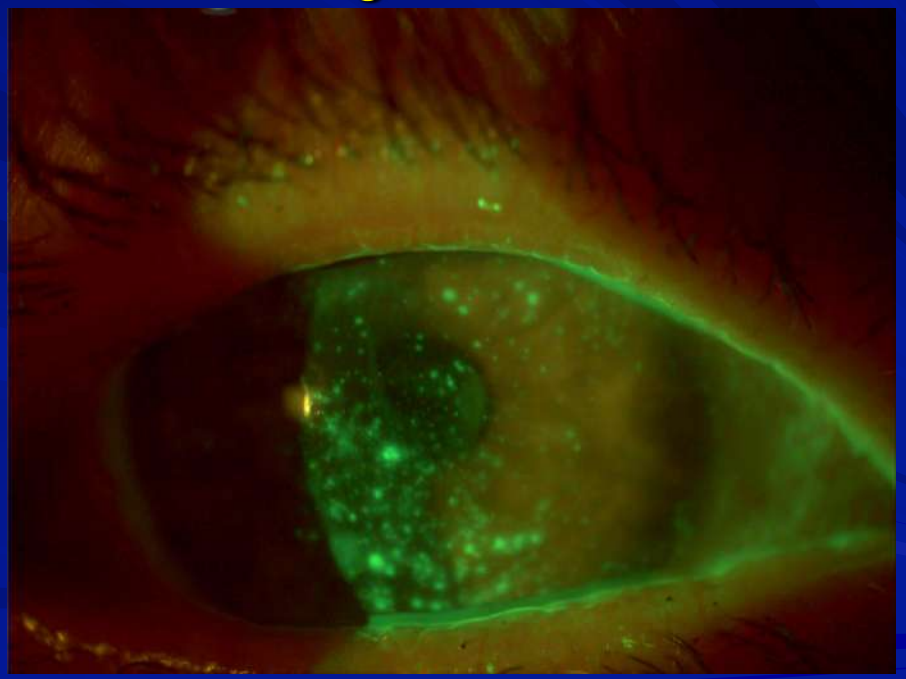


Mackie Classification

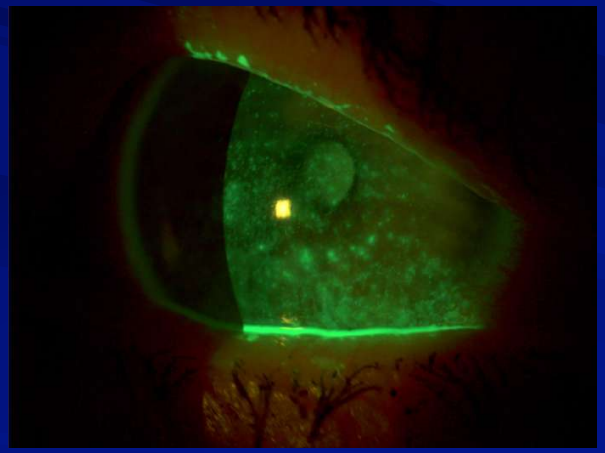
Moderate - Stage 2



Moderate - Stage 2



Resolved



Oxervate™ (cenegermin-bkbj)

- Approved 2018 (August 28, 2018)
- Dompé farmaceutici SpA
- Ophthalmic solution indicated for the treatment of neurotrophic keratitis
- Dosing: Instill 1 drop in affected eye 6 times per day (at 2-hour intervals) for 8 weeks
  - Used as eye drop
    - Not infused or injected
- Storage issues: in the freezer at the pharmacy
  - Patient keeps the individual vials in the fridge – once "actively ready" for use, then it is only stable for 12 hours
- Contraindications
  - None

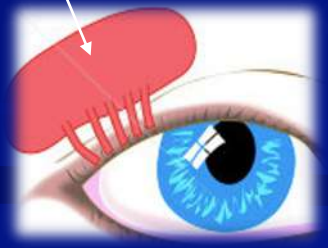
Dompé Team

Corneal Homeostasis

Interaction between corneal nerves and epithelial cells/keratocytes mediates corneal homeostasis

Corneal nerves stimulate blinking and tear production

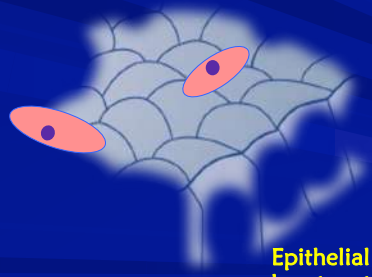
Tear gland



Tear secretion

Tears contain growth factors and nutrients that stimulate epithelial cells

Neurotrophins, neuropeptides and growth factors (e.g., NGF) from epithelial cells and keratocytes mediate nerve fibre survival, differentiation and maturation



Epithelial cells and keratocytes

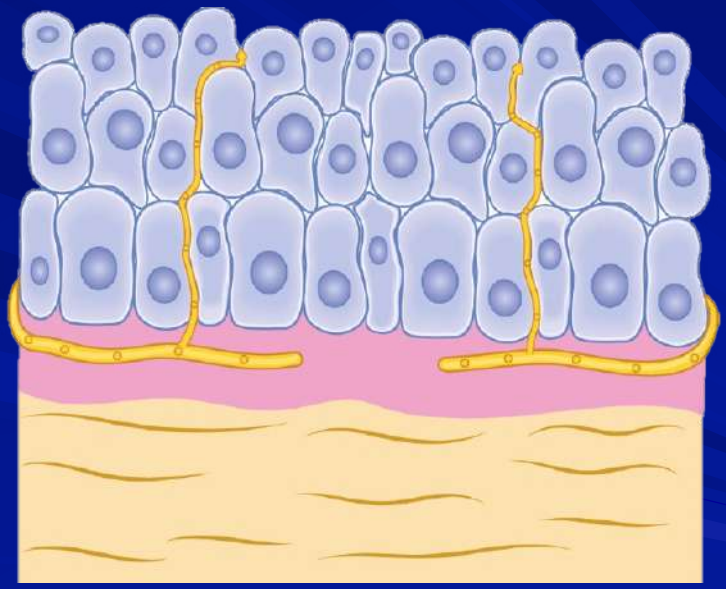
Neuromediators provide trophic support to ocular surface tissues (particularly epithelial cells & keratocytes) that:

- Stimulates wound healing
- Maintains anatomic integrity

Adapted from Mastropasqua L, et al. J Cell Pathol. 2017;232:717–24.

Pathophysiology of NK[1]

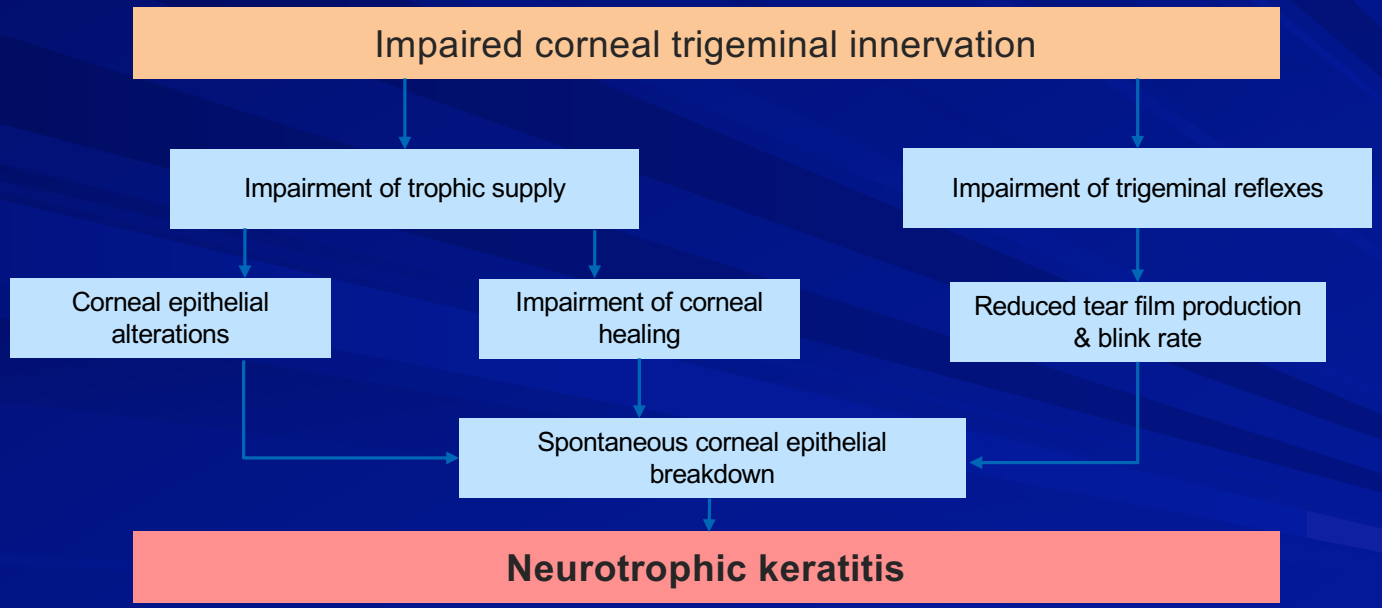
- The loss of corneal sensory innervation via damage to the trigeminal nerve reduces release of neuromediators that provide trophic (nutritional) support to the ocular surface tissues, stimulate wound healing and maintain anatomic integrity
- Impairment of corneal sensitivity also affects tear film production and blink rate due to the reduction of trigeminal reflexes
- Impairment of trigeminal innervation leads to decreased corneal epithelium renewal and healing rate, and ultimately the development of NK



Penetration of nerves into the epithelium

1. Mastropasqua L, et al. J Cell Pathol. 2017;232:717–24; 2. Müller LJ, et al. Exp Eye Res. 2003;76:521–42.

Trigeminal nerve damage leading to NK[1]



Adapted from 1. Mastropasqua L, et al. J Cell Pathol. 2017;232:717–24.

Etiologies Associated with NK

Ocular
- Herpes (simplex or zoster) infection
- Other infections e.g acanthamoeba
- Chemical or physical burn
- Abuse of topical anaesthetics
- Drug toxicity
- Chronic ocular surface injury or inflammation
- Ocular surgery
- Cataract surgery
- LASIK, PRK
- PK and DALK
- Collagen crosslinking for keratoconus
- Vitrectomy for retinal detachment
- Photocoagulation for diabetic retinopathy
- Postsurgical or laser treatment
- Routine laser for proliferative diabetic retinopathy
- Contact lenses
- Orbital neoplasia
- Corneal dystrophies

Central nervous system
- Neoplasm
- Aneurysms
- Stroke
- Degenerative CNS disorders
- Post-neurosurgical procedures
  - For acoustic neuroma
  - For trigeminal neuralgia
- Other surgical injury to trigeminal nerve

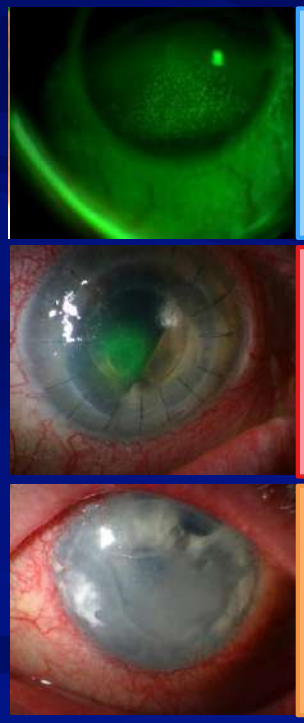
Systemic
- Diabetes mellitus
- Leprosy
- Vitamin A deficiency
- Amyloidosis
- Multiple sclerosis

Genetic
- Riley-Day syndrome (familial dysautonomia)
- Goldenhar-Gorlin syndrome
- Mobius syndrome
- Familial corneal hypoaesthesia

DALK=deep anterior lamellar keratoplasty; LASIK=laser in situ keratomileusis; PK=penetrating keratoplasty; PRK=photorefractive keratectomy

1. Dua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003.

NK classification



Stage 1: Mild

(Epithelial changes only without epithelial defect): Epithelial irregularity without frank epithelial defect, tear film instability and symptoms (hyper-aesthesia) with reduced or absent sensations in one or more quadrants of the cornea

Stage 2: Moderate

(Epithelial defect without stromal defect): Frank persistent epithelial defect and corneal hypo-aesthesia/ anaesthesia

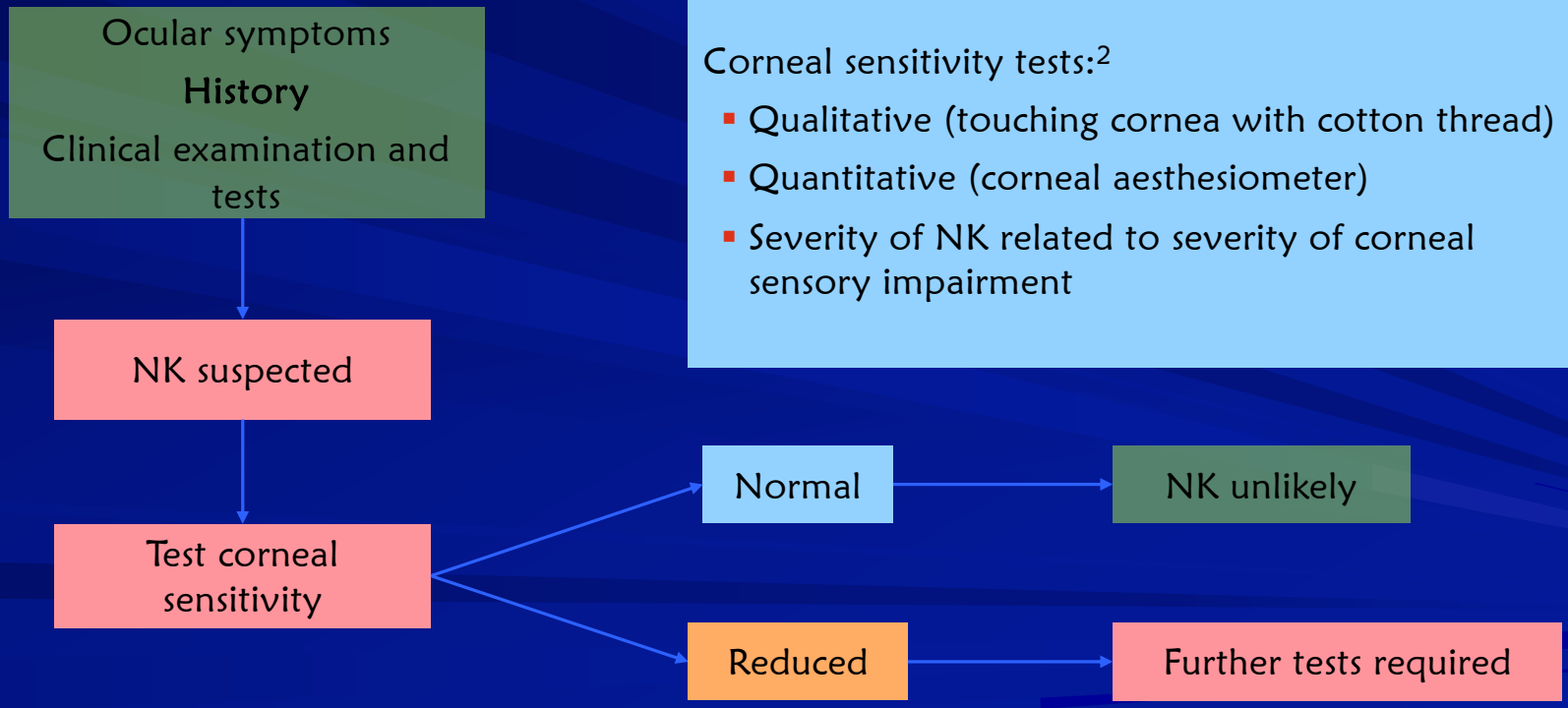
Stage 3: Severe

(Stromal involvement): Stromal involvement from corneal ulcer to lysis to perforation, with corneal hypo-aesthesia/anaesthesia

Images by kind consent of Prof. Messmer and Prof. Dua

1. Dua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003. [Epub ahead of print]. 2. 1. Semarero F, et al. Ophthalmologica 2014;231:191–7; 2. Sacchetti M & Lambiase A. Clin Ophthal 2014:8 571–9.

Assessment of Corneal Sensitivity is Essential to Confirm NK diagnosis[1]



Corneal sensitivity tests:[2]

- Qualitative (touching cornea with cotton thread)
- Quantitative (corneal aesthesiometer)
- Severity of NK related to severity of corneal sensory impairment

Adapted from 1. Dua HS, et al. Prog Retin Eye Res. 2018 doi: 10.1016/j.preteyeres.2018.04.003. [Epub ahead of print]; 2. Sacchetti M & Lambiase A. Clin Ophthal 2014:8 571–9.

Endogenous NGF maintains corneal integrity by three mechanisms

Endogenous Nerve growth factor acts through specific high-affinity (i.e., TrkA) and low-affinity (i.e. p75NTR) nerve growth factor receptors in the anterior segment of the eye to support corneal innervation and integrity.[1]

SHOWN IN PRECLINICAL MODELS[1]

CORNEAL INNERVATION

NGF plays a role in nerve function and stimulates the regeneration and survival of the sensory nerves[2,3]

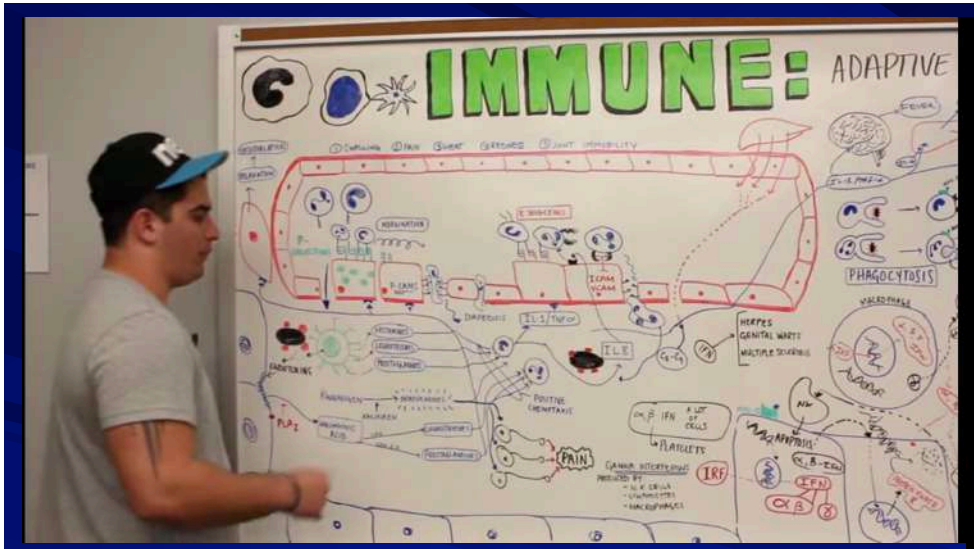
TEAR SECRETION

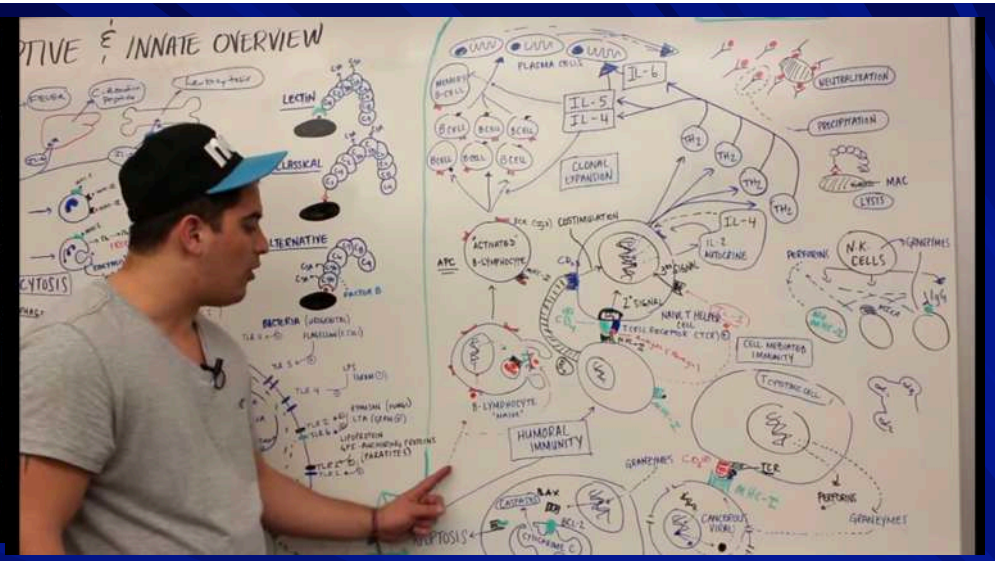
NGF binds receptors on lacrimal glands and promotes sensory-mediated reflex tearing secretion[1,4]

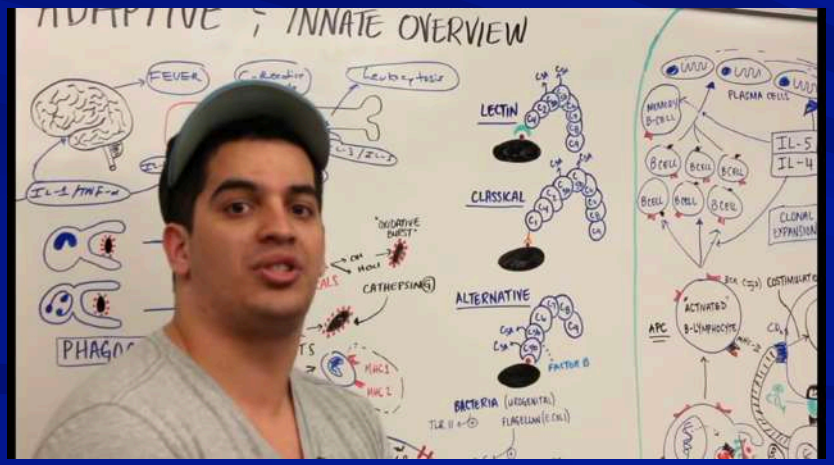
CELL PROLIFERATION AND DIFFERENTIATION

NGF stimulates proliferation, differentiation, and survival of corneal epithelial cells[1]

1. Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol.* 2017 Apr;232(4):717-724. 2. Müller LJ, Marfurt CF, Kruse F, Tervo TM. Corneal nerves: structure, contents and function. *Exp Eye Res.* 2003 May;76(5):521-42. 3. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol.* 2014;8:571-9. 4. Muzi S, Colafrancesco V, Sornelli F, et al. Nerve Growth Factor in the Developing and Adult Lacrimal Glands of Rat With and Without Inherited Retinitis Pigmentosa. *Cornea.* 2010;29:1163–1168







A different biologic

Ninja Nerd Science
YouTube

Biologic Drugs

- Biologic therapies include wide range of medical products
  - First-generation biologic therapies
    - Vaccines
    - Blood products
    - Stem cell injections
- Today, when people talk about "biologics" they usually mean the second-generation biologic therapy drugs
  - Humira, Remicade, Enbrel

- Biologic therapies
  - Cannot be made using a simple chemical reaction
    - Mixing ingredients together in a laboratory, the way conventional drugs are made
  - Are made using living organisms

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Question?

Biologic drugs are:

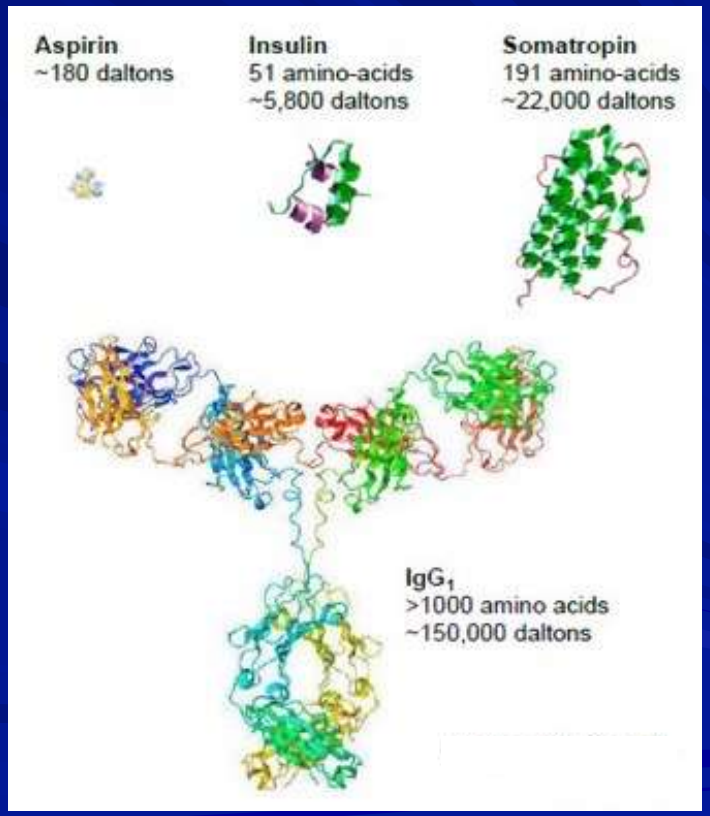
A. Large molecules
B. Small molecules
C. Nano-particles (super small molecules)
D. I don't know, that is why I am here

Small Molecule Drugs versus Biologics

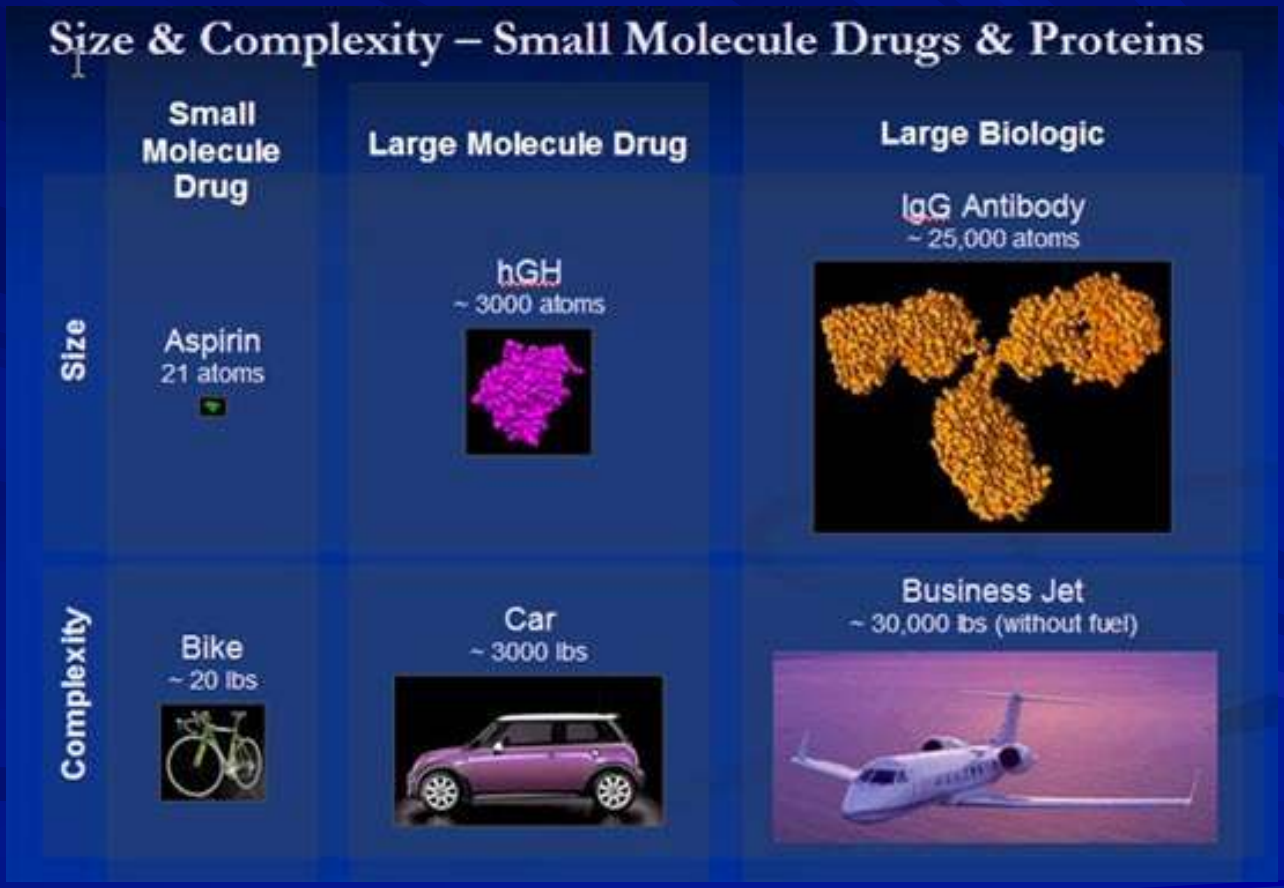
- Small molecule drugs are made by adding and mixing together known chemicals and reagents using a series of controlled and predictable chemical reactions
  - Organic chemistry
  - Inorganic chemistry
- Biologics are made by harvesting the substances produced and secreted by constructed cells
  - Genetic engineering – is the closet manufacturing process of a biologic drug

Biologic Drugs versus Small Molecule Drugs

- Biologic Drugs
  - Larger, complex, dynamic structures
  - Diverse populations of molecules
    - Not easily characterized
  - Complicated manufacturing
  - Example: Teprotumumab (Tepezza)
- Small Molecule Drugs
  - Synthetic
  - Manufactured using a defined chemical process
  - Smaller and simpler
  - Example: Aspirin



Size and Complexity of Biologic Drugs



https://www.azbio.org/small-molecules-large-biologics-and-the-biosimilar-debate

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Question?

Biologic drugs are produced by inserting DNA into:

A. Yeast
B. Bacteria
C. Virus
D. All the above
E. I don't know, that is why I am here

Making Biologics

A piece of DNA is inserted into a living cell— yeast, bacterial, viral, or mammalian cell

↓

Cell then produces a large amount of a specific molecule (e.g. protein)

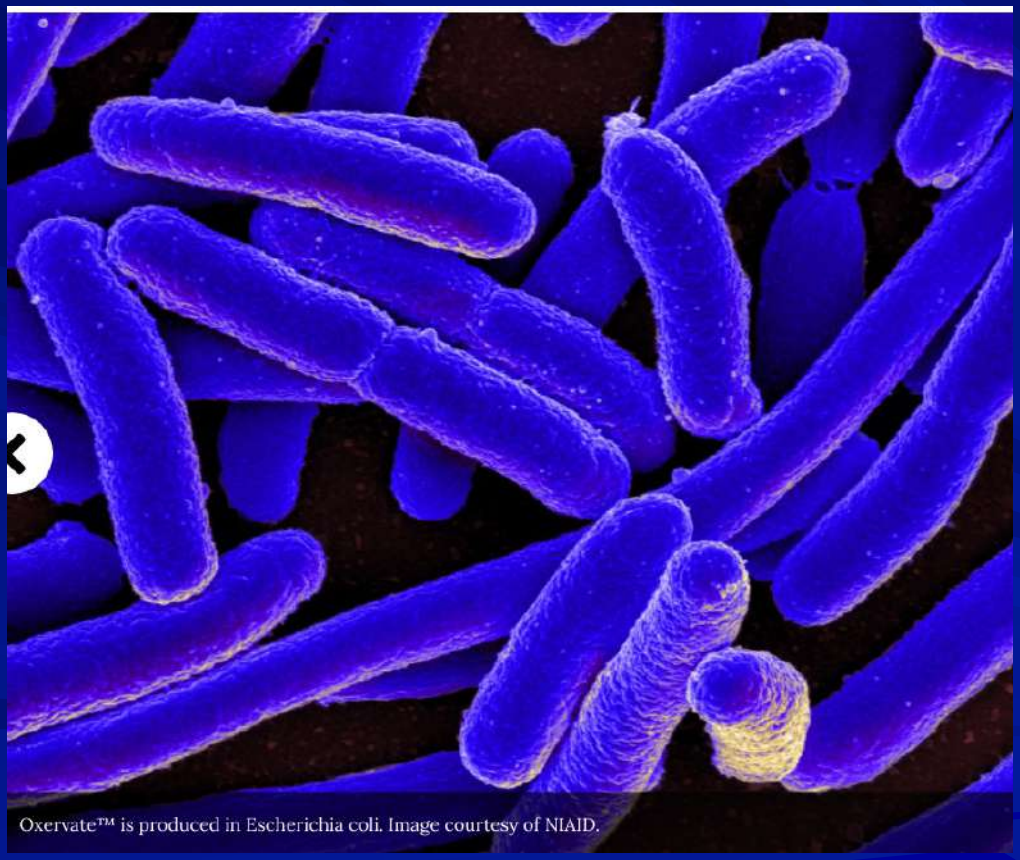
↓

Desired molecular isolation (living cells/material removed - only the desired molecules are left)

↓

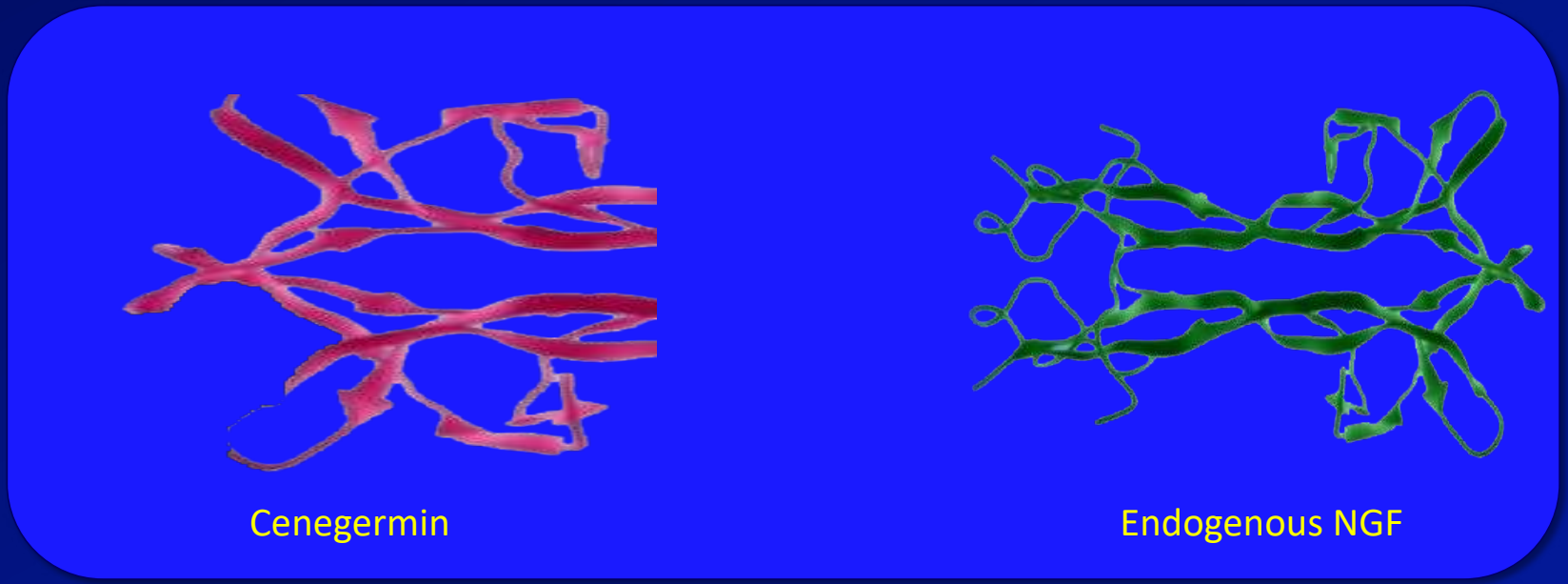
The isolated molecules become the active ingredient in a biologic drug

Escherichia Coli



Oxervate™ is produced in Escherichia coli. Image courtesy of NIAID.

Cenegermin Mimics the Structure of Endogenous NGF in the Ocular Tissues

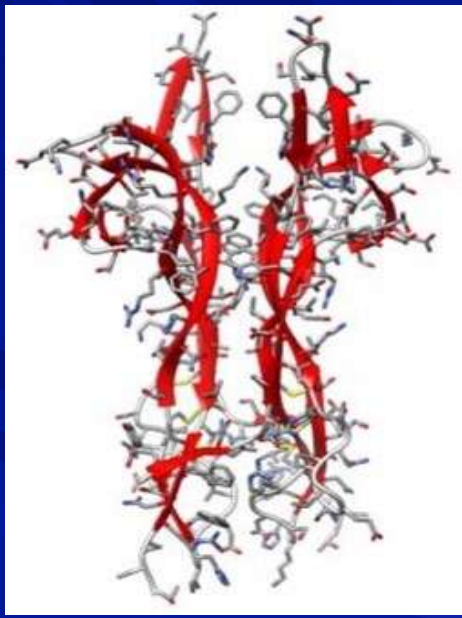


Cenegermin-bkbj, the active ingredient in the FDA-approved OXERVATE™ (cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL), is structurally identical to the human NGF protein found in ocular tissues

Voelker R. New Drug Treats Rare, Debilitating Neurotrophic Keratitis. JAMA. 2018;320(13):1309.

Active ingredient structurally identical to human nerve growth factor produced in ocular tissues

- Naturally occurring neurotrophin is responsible for differentiation, growth, and maintenance of neurons[1]
- The regenerative potential of nerve growth factor (NGF) was discovered by Nobel-prize winning scientists in the early 1950s[1]
- Cenegermin-bkbj, a novel recombinant human nerve growth factor (rhNGF), is **STRUCTURALLY IDENTICAL** to the NGF protein[2]



1. Lambiase A, Rama P, Bonini S, Caprioglio G, Aloe L. Topical treatment with nerve growth factor for corneal neurotrophic ulcers. *N Engl J Med* 1998;338:1174-80. 2. Voelker R. New Drug Treats Rare, Debilitating Neurotrophic Keratitis. JAMA. 2018;320(13):1309.

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% Weekly Device Kit

- OXERVATE™ is supplied in a weekly carton containing 7 multiple-dose vials*
- A separate weekly Delivery System Kit contains the supplies needed to administer treatment

The Delivery System Kit Contains:

- 7 vial adapters
- 42 pipettes
- 42 sterile disinfectant wipes
- 1 dose recording card
- 1 extra adapter, 3 extra pipettes, 3 extra wipes are included as spares

- **Extra drug is available in each vial to take into consideration for loss or spillage during treatment administration*

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.

OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002%
Dosing and Administration

Instill 1 drop of OXERVATE™
(cenegermin-bkbj) ophthalmic solution 0.002%
in the affected eye(s)

Every 2 hours

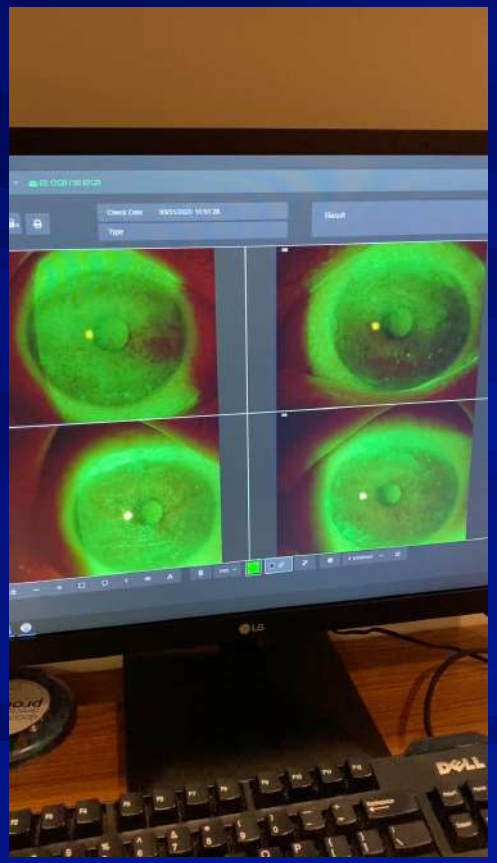
Apply 6 times daily

Continue for 8 weeks

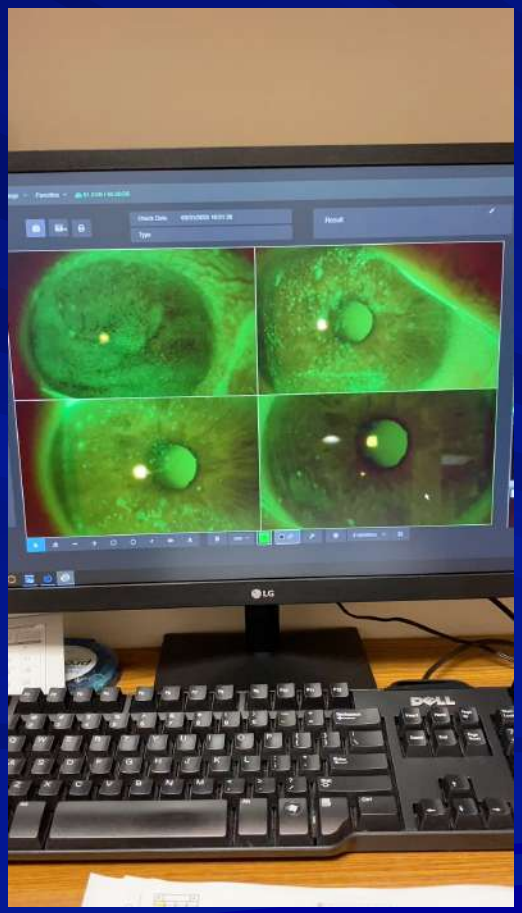
OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.

Let's Hear From a Patient

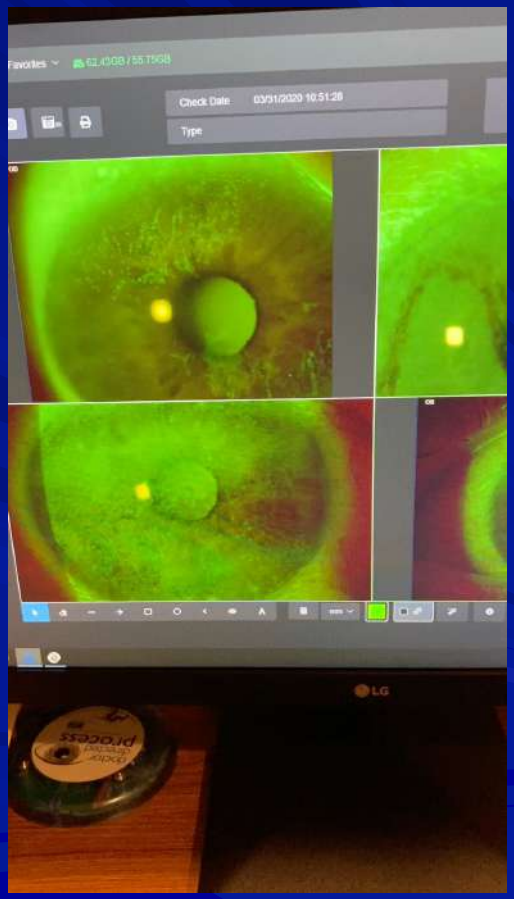
April 7, 2020 - After 1 week



April 21, 2020 - After 3 weeks



May 12, 2020 - After 6 weeks



Study Conclusions

After 8 weeks of treatment, 6 times daily

In the majority of patients across two clinical studies OXERVATE™ (cenegermin ophthalmic solution 0.002%) was well tolerated and more effective than vehicle in promoting complete corneal healing of moderate or severe NK.

Study NGF0212 (REPARO) (N=52 per group)
European patients with NK in one eye

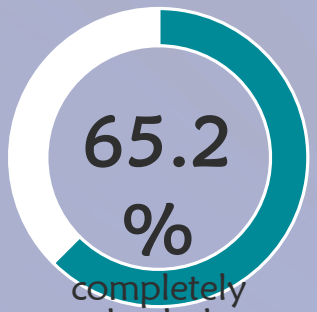
NCT01756456

Vehicle response rate 33.3%

Study NGF0214 (N=24 per group)

U.S patients with NK in one or both eyes

NCT02227147



Vehicle response rate 16.7%

Of patients who healed after one 8-week course of treatment…

80 %

Remained healed for one year*

*Based on REPARO, the study with longer follow-up

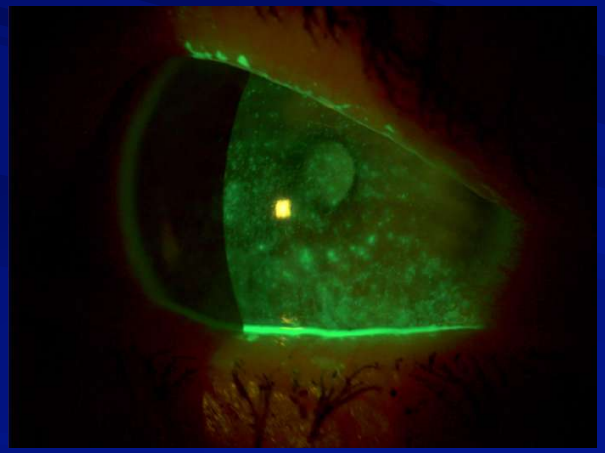
Safety: The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1-10% of OXERVATE™ patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation and tearing[3]

1. Bonini S, Lambiase A, Rama P et al. Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. Ophthalmology. 2018;125:1332-1343. 2. Chao W, J. BOC, R. D. et al. Data on file. Healing of persistent epithelial defects or corneal ulcers by recombinant human nerve growth factor eye drops in patients with stage 2 or 3 neurotrophic keratitis. Presented at: Congress of the European Society of Ophthalmology (SOE) 10–13 June, 2017, Barcelona, Spain. 2017. 3. OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.

OXERVATE™ (cenegermin-bkbj)

- Adverse reactions: very well tolerated
- The most common adverse reaction in clinical trials
  - eye pain, corneal deposits, foreign body sensation in the eye, ocular hyperemia, swelling of the eye, and increase in tears
- Contact lenses (therapeutic or corrective) should be removed before applying cenegermin
  - presence of a contact lens may limit the distribution of cenegermin-bkbj onto the corneal lesion
  - Lenses may be reinserted 15 minutes after administration.

Crime and Punishment Match



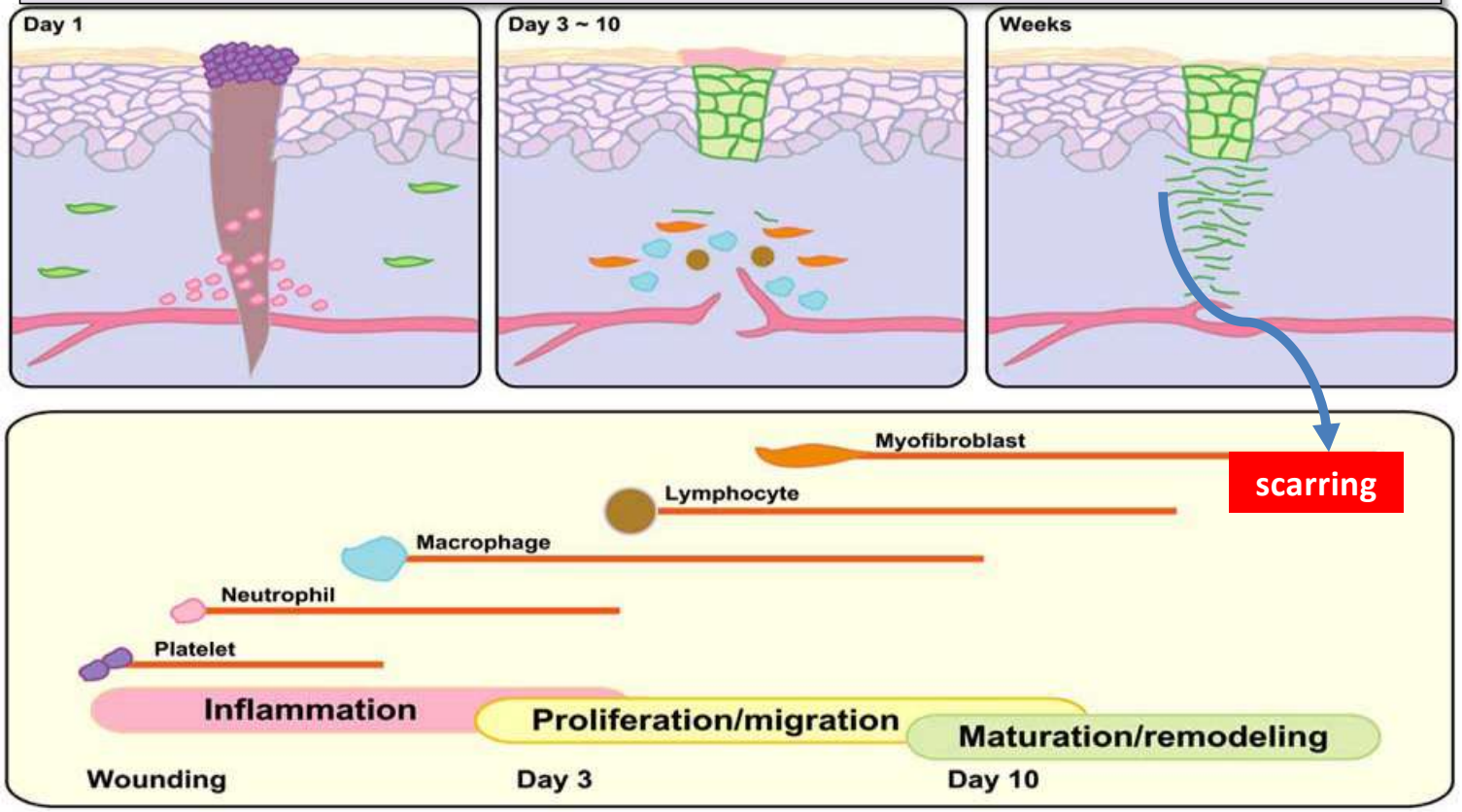
Amniotic Membrane

Alternative or

While waiting for Oxervate

Adult Wound Healing

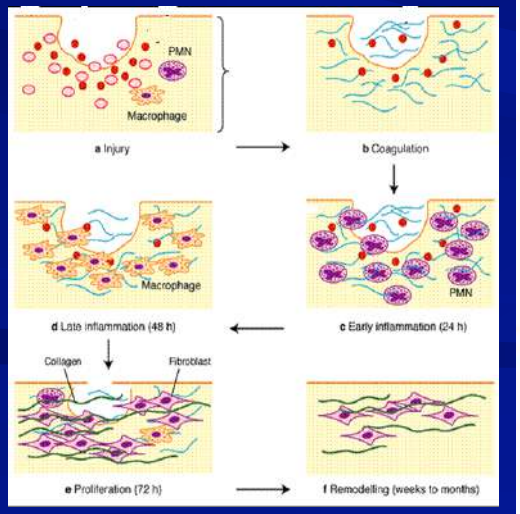
Insight into the Relationship between "Inflammation" and "Regeneration"

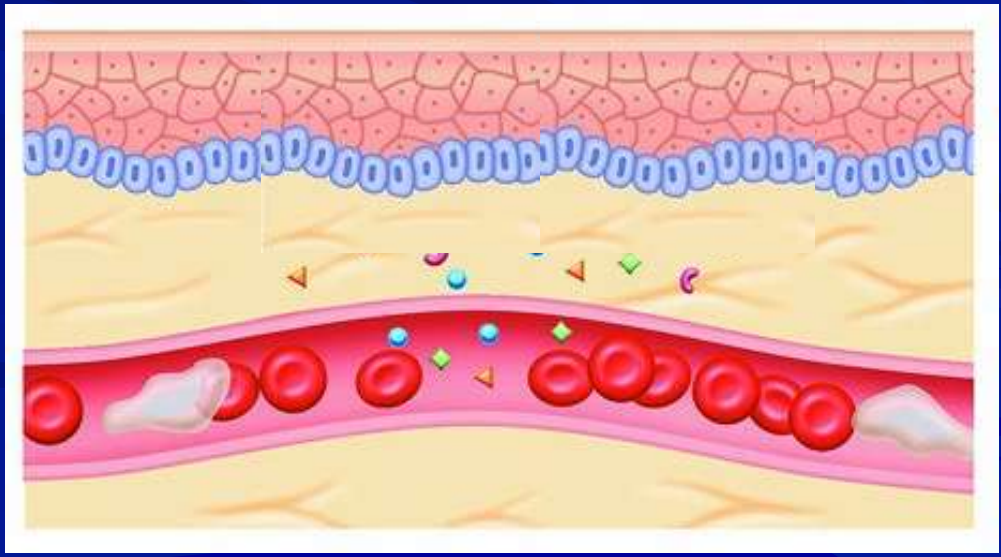


Shaw et al, *Endocrine, Metabolic & Immune Disorders - Drug Targets*, 10:320-330, 2010

Regeneration vs. Repair

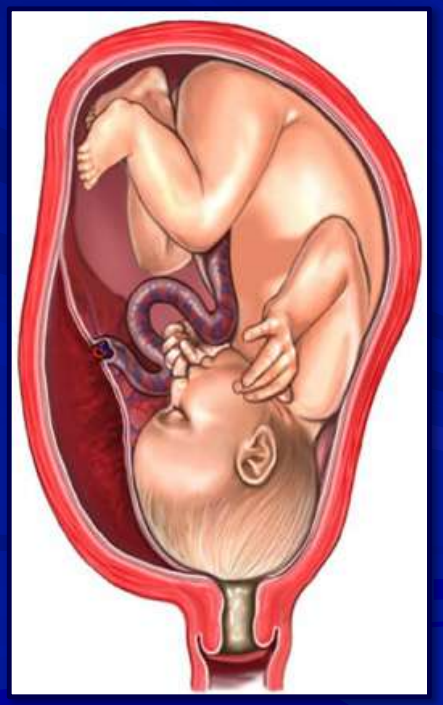
- Regeneration = cells/tissue reproduction = NO SCAR
- Repair= Healing by granulation tissue / scar formation
  - Scarring correlates directly with Inflammation
  - Controlling Inflammation → Reduces Scarring



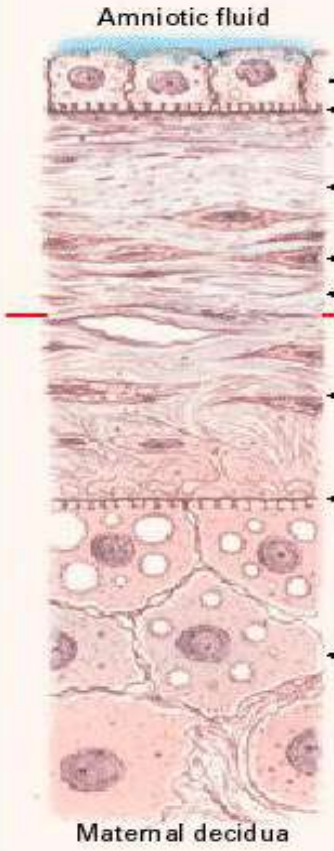


Amniotic Membrane
Regenerative Wound Healing

- Amniotic membrane shares the same cell origin as the fetus
  - Stem Cell behavior
- Structural similarity to all human tissue
  - Tissue replacement/ Less granulation
- Regenerative tissue response away from:
  - Inflammation
  - Angiogenesis
  - Scarring
  - Rejection



Structure of the Fetal Membrane

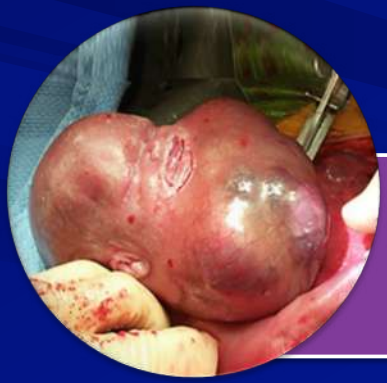


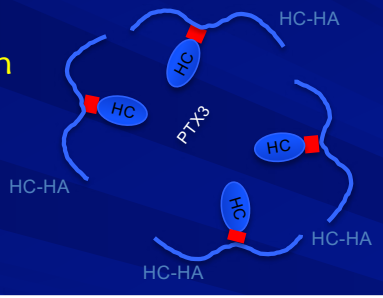
Layer	Extracellular-Matrix Composition
Amnion	
Epithelium	
Basement membrane	Collagen types III, IV, V; laminin, fibronectin, nidogen
Compact layer	Collagen types I, III, V, VI; fibronectin
Fibroblast layer	Collagen types I, III, VI; nidogen, laminin, fibronectin
Intermediate (spongy) layer	Collagen types I, III, IV; proteoglycans
Chorion	
Reticular layer	Collagen types I, III, IV, V, VI; proteoglycans
Basement membrane	Collagen type IV; fibronectin, laminin
Trophoblasts	

Scarless Fetal Wound Healing

Speed & Quality of Healing Count!

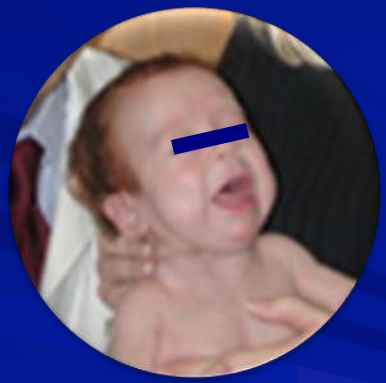
Giant neck mass resection
at 26 weeks *in-utero*





HC-HA/PTX3, found naturally in amniotic membrane, is the critical biologic component responsible for scarless fetal wound healing.

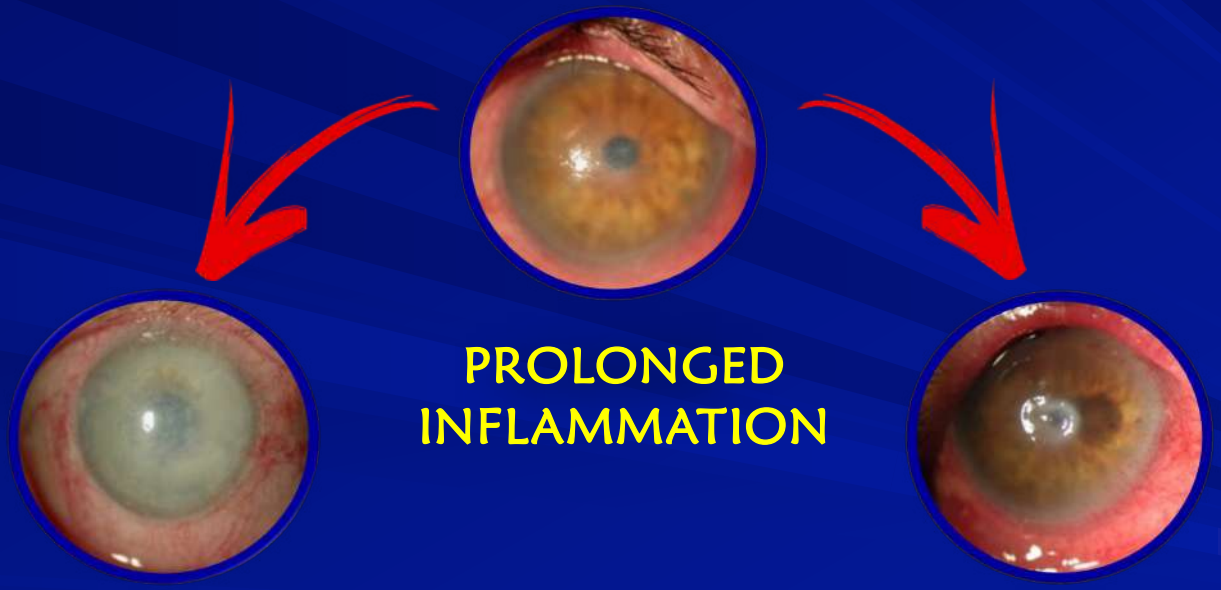
3 months



Courtesy of fetal surgeon, Michael Harrison, M.D. (UCSF)

Normal Adult Wound Healing

Our body does not achieve state-of-the-art healing on its own…



PROLONGED INFLAMMATION

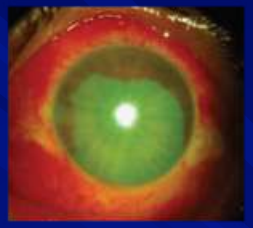
RESIDUAL HAZE

SCAR FORMATION

Exposure keratitis

Tissue injury

Chemical burn



Damage

Inflammation

Keratocyte activation

Fibroblast differentiation to myofibroblast

Scar formation

Scarless healing

Impaired vision

Clear vision

Healing with Scar Formation

Healing without Scarring

Sutureless Amniotic Membrane
wound healing vs wound covering

- Cryopreserved- wound healing
  - PROKERA- BioTissue
- Dehydrated- wound covering
  - AmbioDisk -IOP Ophthalmics- Ketena
    - Single layer, shiny/matte side
  - BioD – BioD Optix
    - Single layer, IOP for proper side
  - Aril- Seed Biotech/Blythe Medical
  - Eclipse- Ophthalogix
    - Single and dual layer
    - 45 microns of amnion, increased tensile strength

Dehydrated AM

- Preserved using vacuum
- Low temperature heat
  - To retain devitalized cellular components
- FDA-approved claims for this type of AM are limited to wound coverage
  - Wound covering versus wound healing
- Kept at room temperature
- Must be rehydrated for clinical use

Dehydrated AM

- Requires additional tools
  - Lid speculum
  - Weck-Cel sponge
  - Bandage contact lens
- A bandage lens must be placed on top of the membrane to keep it fixated.
  - Some dehydrated AMs are packaged along with a contact lens
  - These AMs cannot be used with any bandage lens
    - Only the accompanying lens

PROKERA®

- Original version which some patients may prefer

PROKERA® | Slim

- The most commonly used
- Ideal for DED with keratitis
- Slimmest ring for improved comfort

PROKERA® | PLUS

- Double layer CAM for severe indications such as severe DED, Ulcers, Chemical Burns, SJ, Sjögren's

PROKERA® | Clear

- Same design as Slim, but with aperture for improved vision during treatment

- Larger CAM used in various surgical procedures such as Pterygium, CCh, and SLK

- Umbilical Cord membrane used in various surgical procedures such as Glaucoma shunt tube covering

The donor has been screened for the following infectious diseases

- HIV-1 & HIV-2 Antibody
- HIV-1 (RNA-NAT)
- Hepatitis B Surface Antigen (HBsAg)
- Hepatitis B Core Antibody (HBcAb)
- Hepatitis B Virus (HBV, DNA-NAT)
- Hepatitis C Antibody (HCVAb)
- Hepatitis C Virus (HCV, RNA-NAT)
- Syphilis (RPR)
- HTLV I & II Antibody (HTLV I/II Ab

- A blood specimen, drawn within ±7 days of donation
  - FDA or CMS guidelines
- Microbial testing has also been performed on the final product to identify
  - Aerobic
  - Anaerobic
  - Fungal

Amniotic Membrane Components

- Proteoglycans
- Growth factors
- Collagens (types I, III, IV, V and VI)
- Fibronectin
- Laminin
- Heavy chain hyaluronic acid (HC-HA)
- PTX 3 (HC-HA Complex)
  - ★ Pentraxin 3

Direct inhibition of pro-inflammatory cells[4,5]

- Suppresses T-cell activation
- Inhibits giant cell formation
- Controls MMP production[7]

Insertion of Prokera
Minor Surgery

Bio Optix

Amniotic Extracellular Matrix

BioD

Allograft Tissue Information and Product Preparation Insert

Contents / How Supplied

This package contains Human Cellular and Tissue Based Products (HCT/P) as defined by US FDA 21 CFR Part 1271.

CAUTION:

Federal (USA) law restricts this product to sale by or on the order of a licensed physician.

The **Donated Human Tissue** has been determined eligible for transplantation by a licensed Medical Director according to the criteria listed in the Donor Selection section below.

Product Description

BioDOptix™ is a human amnion membrane allograft provided in prescribed geometric configurations. BioDOptix is dehydrated during processing and should be dry when the package is opened. The inner peel pouch and tissue product are terminally sterilized via E-beam irradiation and may be placed directly into the sterile field. Included in the packaging along with this insert are a Tracing Record and a set of patient labels.

- BioDOptix is sterilely packaged for single patient, one time use only.
- Once opened, BioDOptix must be used immediately or discarded.

Introduction

BioDlogics, LLC, is registered with the Food and Drug Administration (FDA) as a manufacturer and distributor of human cells, tissue, and cellular and tissue-based products (HCT/P). All donor recoveries are performed by BioRecovery, LLC, an affiliate of BioDlogics, LLC. BioRecovery, LLC is also registered with the FDA and adheres to the regulations regarding HCT/P recovery and the screening and testing of the tissue donor as verified through supplier audits.

Donor Selection

The Medical Director of the registered recovery agency has determined that the donor of the tissue contained in this product is eligible to donate tissue for transplantation based on meeting the following criteria:

1. **The results of donor screening indicated that the donor was free from risk factors for and clinical evidence of infection due to relevant communicable disease agents and diseases, and**
2. The results of donor testing for the following relevant communicable disease agents are negative or non reactive:
   - Antibodies to the human immunodeficiency virus type 1and type 2 (anti-HIV-1 and anti-HIV-2)
   - HIV-1/Hepatitis B/Hepatitis C by Transcription Mediated Amplification
   - Hepatitis B surface antigen (HBsAg)
   - Hepatitis B total core antibody
   - antibodies to the hepatitis C virus (anti-HCV)
   - Antibodies to human T-lymphotropic virus type I and type II (anti-HTLV-I and anti-HTLV-II)
   - Syphilis using FDA-licensed tests. If the blood sample to be used for syphilis screening is determined and documented to be unacceptable for the screening assay (e.g. hemolysis, sample testing time restriction) then an FDA-licensed treponemal-specific confirmatory assay may be performed instead (e.g. FTA-Abs).

All laboratories performing these tests are certified to perform testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and 42 CFR part 493 or have met equivalent requirements as determined by the Centers for Medicare and Medicaid Services (CMS).

At the time of recovery, cultures of the tissue are taken and grown out for evaluation. Additionally, a donor's medical history and behavior risk assessment, incorporating U.S. Public Health Service guidelines, are obtained prior to donation. Discussions with physicians and/or the donor mother are conducted to identify circumstances that may lead to the exclusion of the donor or donated tissue. The blood sample test results, donor medical history, behavior risk assessment, physical assessment, and information from other sources or records, which may pertain to donor suitability, have been evaluated by a Medical Director. The Medical Director is a licensed physician who completes a comprehensive review of every donor record. The results are used to determine that the donor suitability criteria at the time of tissue recovery have been met, and that the tissue is acceptable for transplantation.

The names and addresses of the testing laboratories, the interpretation of all required infectious disease tests, a listing of the documents reviewed as part of the relevant medical records and all pertinent donor medical information can be quickly retrieved upon request for any allograft tissue recovered on the behalf of BioDlogics, LLC.

Recovery

Tissue recovery is aseptically performed by BioRecovery, LLC, an FDA-registered tissue bank. At the time of recovery, medical records are collected and reviewed as part of donor eligibility.

Processing

BioDOptix is processed by BioDlogics, LLC, in a controlled environment using methods designed to prevent contamination and cross-contamination of the products. Technical quality assurance standards are rigorously maintained. Ethanol is used during processing and trace residuals remain on the product.

Tissue Distribution

BioDOptix is distributed by BioDlogics, LLC.

Tissue Storage

It is the responsibility of the Tissue Dispensing Service and/or end user to maintain BioDOptix in its original packaging and at room temperature until ready for use.

HCT/P Tracking

Important notice to end-user: Recipient records must be maintained for the purpose of tracing tissue post-transplant per The Joint Commission and FDA requirements. The allograft ID number must be recorded in the operative record. The Tracing Record must be completed and returned to BioDlogics, LLC. Patient labels which include tissue numbers are contained in this package to aid in the tracking process.

General Usage

BioDOptix is intended for use as a wound covering. This product is an allograft tissue intended for homologous use at the direction of a physician.

Precautions

1. BioDOptix contains trace amounts of ethanol. It should not be used in patients with known sensitivity to ethanol.
2. In order to reduce the risk of complications, BioDOptix should not be in used the presence of active infection.
3. Although donor tissue is evaluated and processed following strict FDA guidelines, the donor screening methods are limited and may not detect all diseases. As with any allograft, complications at the graft site may occur post operatively that are not readily apparent. These include, but are not limited to:
   - transmission of communicable diseases, including those of unknown etiology
   - transmission of infectious agents such as viruses, bacteria and fungi
   - immune rejection or, or allergic reaction to, implanted HCT/P.

Adverse Reactions

Adverse reactions or outcomes that potentially involve the use of BioDOptix should be reported immediately to the BioDlogics, LLC Customer Service Department.

Recommended Instructions for use of BioDOptix

These recommendations are designed only to serve as a general guideline. They are not intended to supersede institutional protocols or professional clinical judgment concerning patient care.

piece of sterile mesh to facilitate placement of the graft if the surgeon wants to hydrate the graft before application. The mesh reflects the epithelial side of the tissue (surface closest to the fetus).

Preparation Instructions

1. Open carton or box containing BioDOptix and remove the peel-pack.
2. Peel open the outer package and remove the inner foil pouch using aseptic technique.

Note:

-The inner tray and its contents are sterile and may be placed directly into the sterile field.

3. Peel the inner pouch open and place the implant with the accompanying mesh into the sterile field.

Note:

-Care must be taken in transferring/removing the graft from the package as it is lightweight and may be easily displaced.

-The BioDOptix graft is translucent and will look off-white or yellowish on the mesh that is still in contact with allograft.

-It is important to note that the drier the surface to be covered with the graft, the easier the application.

4. Remove the graft from the mesh and place it at the desired location.

If the allograft has been hydrated prior to application, leave the graft on the mesh to aid in placement.Once the graft is positioned in the desired location, grasp a corner of the allograft with forceps to hold it in place while gently peeling off the mesh.

DO NOT LEAVE ANY MESH IN WOUND

5. It is sometimes necessary to gently "brush" or "massage" the thin membrane at the edges to smooth out wrinkles and folds that can occur during graft placement.
6. If removal and replacement are needed, re-apply the mesh for ease of manipulation.
7. After final placement, discard the mesh.

Return Policy

All return orders of BioDOptix require a Return Authorization (RA) number before product may be returned for credit. Please contact the BioDlogics Customer Service Team for more information.

Note: BioDlogics LLC makes no claims concerning the biological properties of allograft tissue. All tissue has been collected, processed, stored, and distributed in compliance with the FDA regulations governing HCT/Ps. Although every effort has been made to ensure the safety of allograft material, current technologies may not preclude the transmission of disease.

Cryopreserved

Indications:

- PROKERA is intended for use in eyes in which ocular surface cells are damaged or underlying stroma is inflamed or scarred. Acting as a self-retaining biologic corneal bandage, PROKERA effectively treats superficial corneal surface diseases by suppressing inflammation and related pain, promoting epithelial healing, and avoiding haze.
- PROKERA is inserted between the eyeball and the eyelid to maintain space in the orbital cavity and to prevent closure or adhesions. Placement of the conformer also enables application of the cryopreserved amniotic membrane to the ocular surface without the need for sutures.
- PROKERA is for single-use only in one patient by an ophthalmologist or optometrist.

Contraindications:

- PROKERA should not be used in eyes with glaucoma drainage devices or filtering bleb.

Precautions:

Location & Temperature	Use After Receipt
Unopened insulated shipping container	Within the expiration date printed on outer shipping box
-80°C → 4°C (-112°F → 39.2°F) Example: ultra-low temperature freezer, standard freezer, or standard refrigerator	Within the expiration date printed on product packaging (shelf-life is 2 years from date of manufacture)

Journal of Ophthalmology
Volume 2017, Article ID 6404918, 10 pages
https://doi.org/10.1155/2017/6404918

Hindawi

Clinical Study

Corneal Nerve Regeneration after Self-Retained Cryopreserved Amniotic Membrane in Dry Eye Disease

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[4]*Florida International University Herbert Wertheim College of Medicine, Miami, FL, USA*
[5]*Research Institute of Ophthalmology, Cairo, Egypt*
[6]*Boston Image Reading Center, Tufts Medical Center, Tufts University School of Medicine, Boston, MA, USA*
[7]*Center for Translational Ocular Immunology, Department of Ophthalmology, Tufts Medical Center, Tufts University School of Medicine, Boston, MA, USA*
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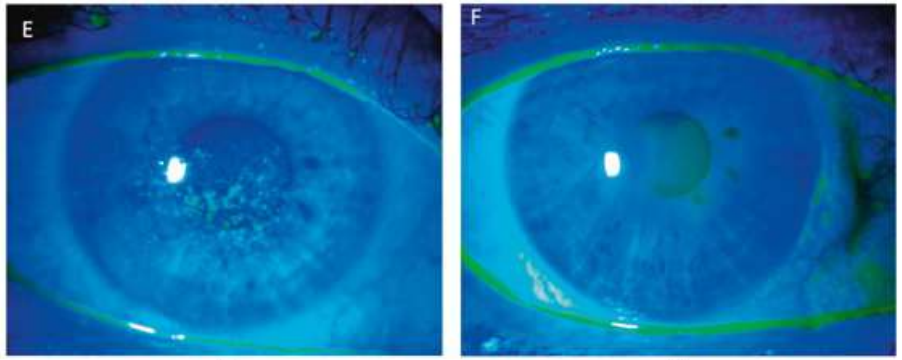
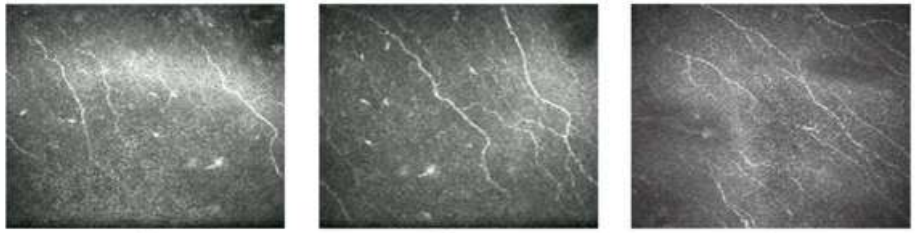
(c) (d)



(e) (f)

Figure 2: Changes in DED severity: pain score (a), SPEED score (b) corneal staining score (c), and DEWS score (d) and an illustrative example of fluorescein staining before (e) and after (f) PKS treatment. Significant decrease in pain score, SPEED questionnaire score, and symptoms in the study group (solid lines) from baseline to 3 months ($p \leq 0.001$), while remained relatively unchanged in the control group (dash lines). * denotes $p \leq 0.05$.



(a) (b) (c)

Figure 5: Illustrative example of IVCM showing the subbasal nerve fiber and dendritiform cells in the study group at baseline (a), 1 month (b), and 3 months follow-up (c).

Optometric Education Consultants

Question and Thank You!

The Non-Healing Cornea Neurotrophic Keratitis

Greg Caldwell, OD, FAAO

Mid-Winter Getaway
Optometric Education Consultants
Sunday, January 28, 2024