Optometric Education Consultants


# The Non-Healing Cornea Neurotrophic Keratitis

Greg Caldwell, OD, FAAO

Mackinac Island Northern Escape
Optometric Education Consultants

Saturday, August 19, 2023

# Disclosures- Greg Caldwell, OD, FAAO

All relevant relationships have been mitigated

- The content of this activity was prepared independently by me - Dr. Caldwell
- Lectured for: B&L, BioTissue, Dompé, Santen
  - Disclosure: Receive speaker honorariums
- Advisory Board: Dompé, Tarsus
  - Disclosure: Receive participant honorariums
- I have no direct financial or proprietary interest in any companies, products or services mentioned in this presentation
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- Envolve: PA Medical Director, Credential Committee
- Healthcare Registries – Chairman of Advisory Council for Diabetes and AMD
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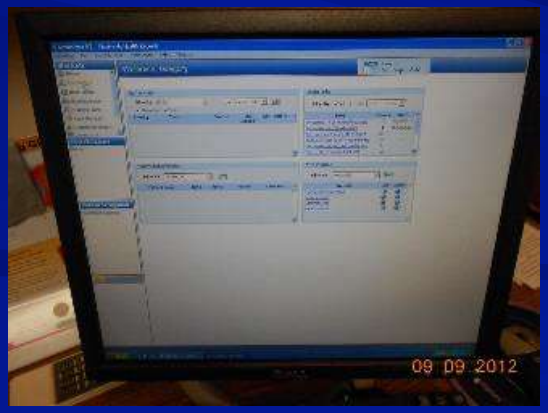
# Financial Obligations

# 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



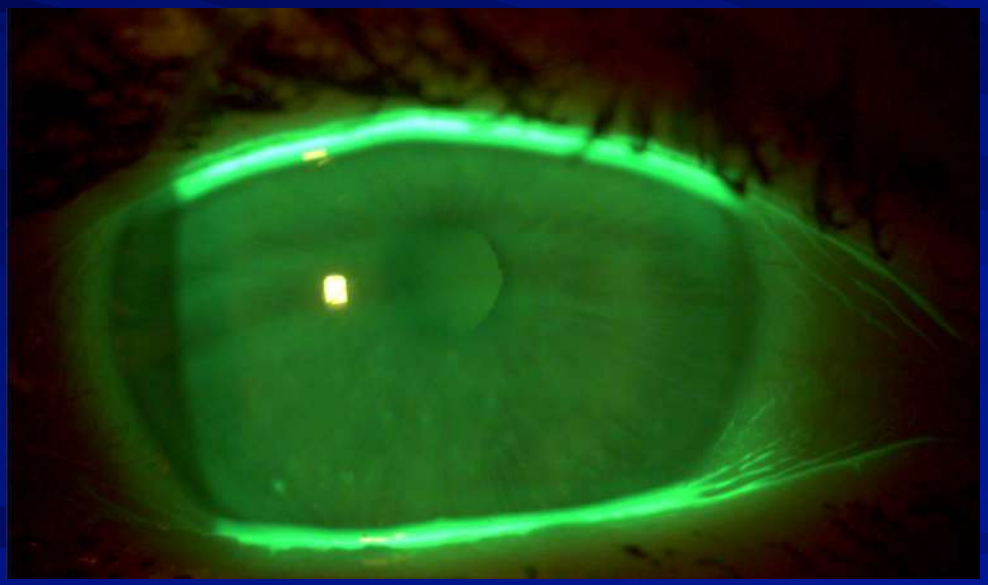


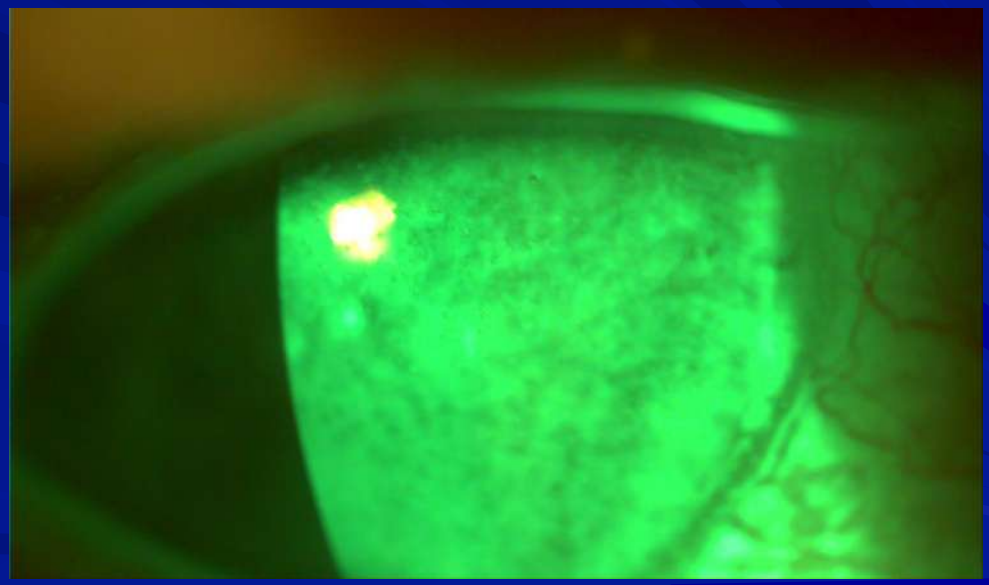


It is wonderful to have someone who's juggling so many aspects of optometry [scientific, clinical experience, teacher & lecturer]. It is refreshing and very informative. -Sarah

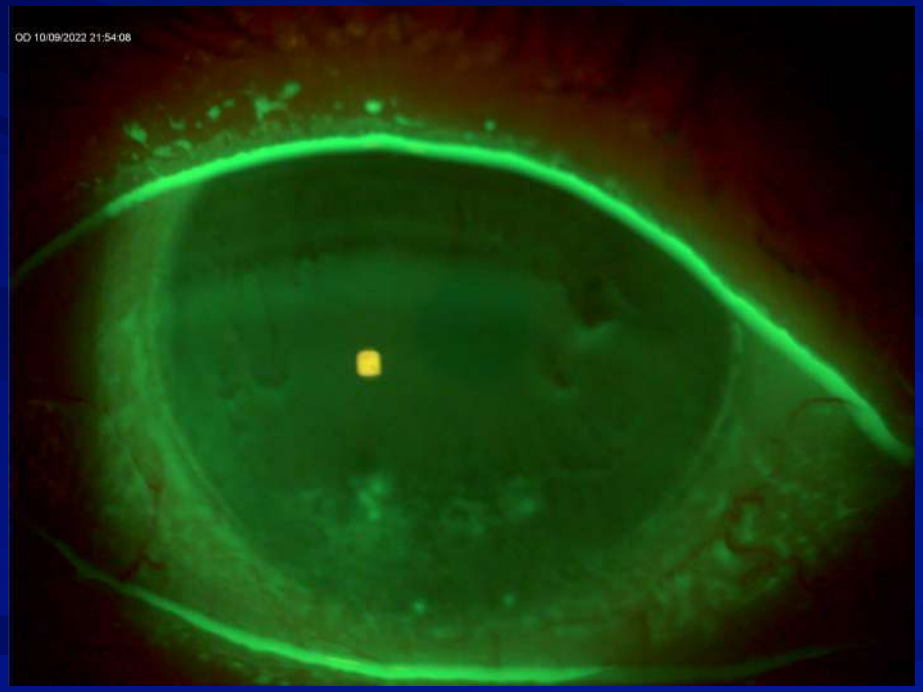
# Which Eye is More Symptomatic?

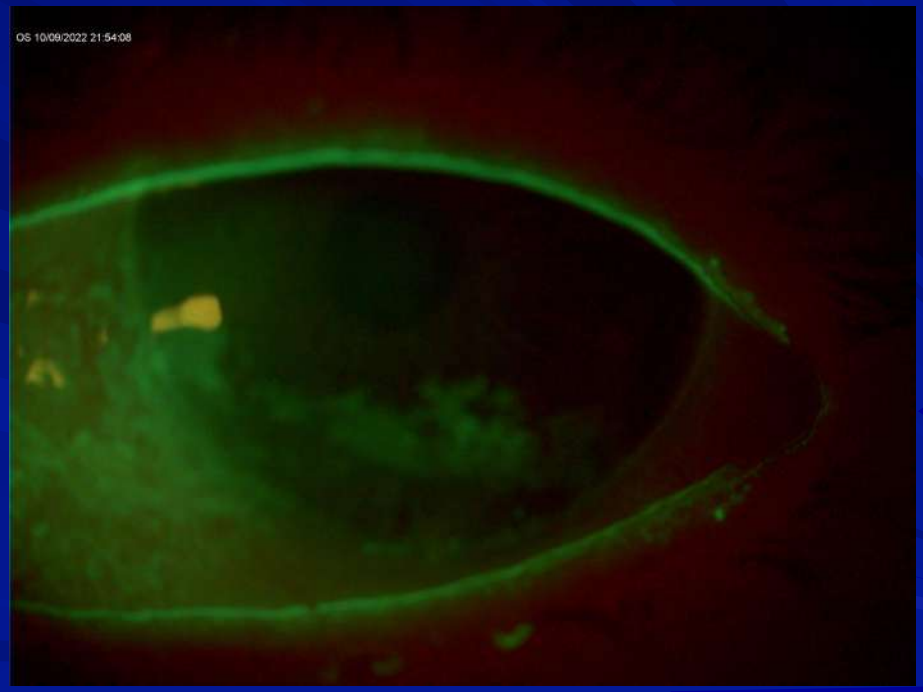
Stain without pain!



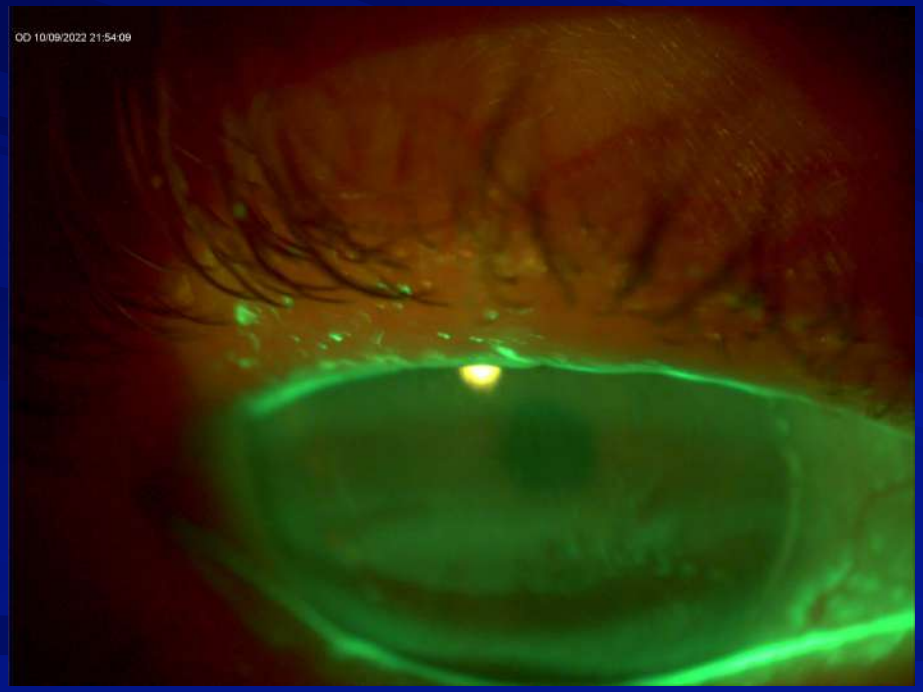


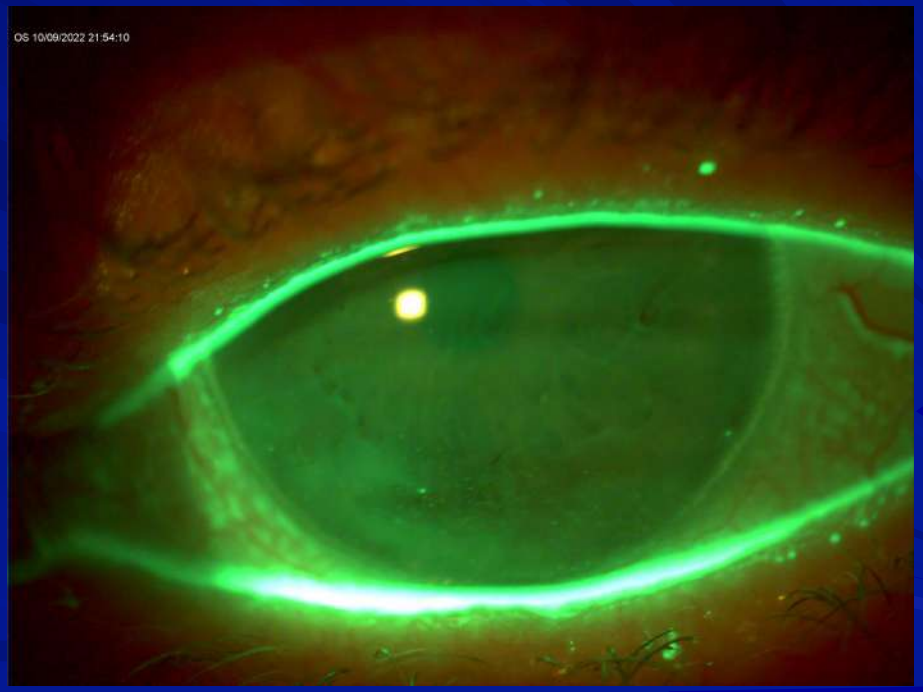
# Before Oxervate™ (cenegermin-bkbj) Treatment



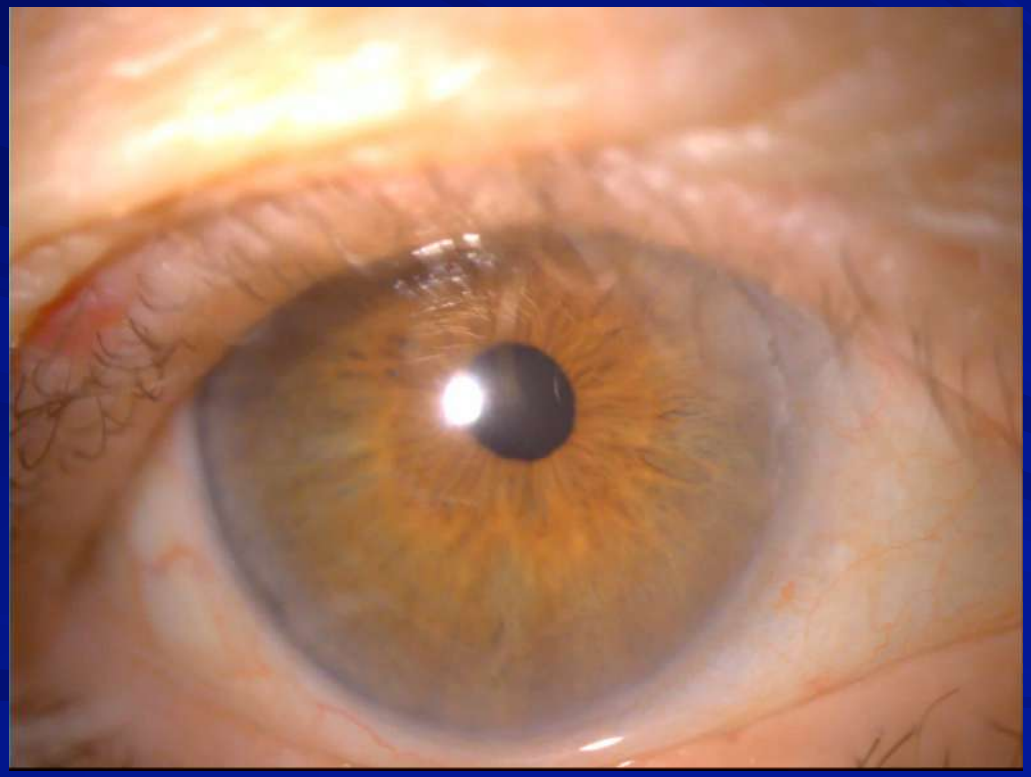
# After Oxervate™ (cenegermin-bkbj) Treatment



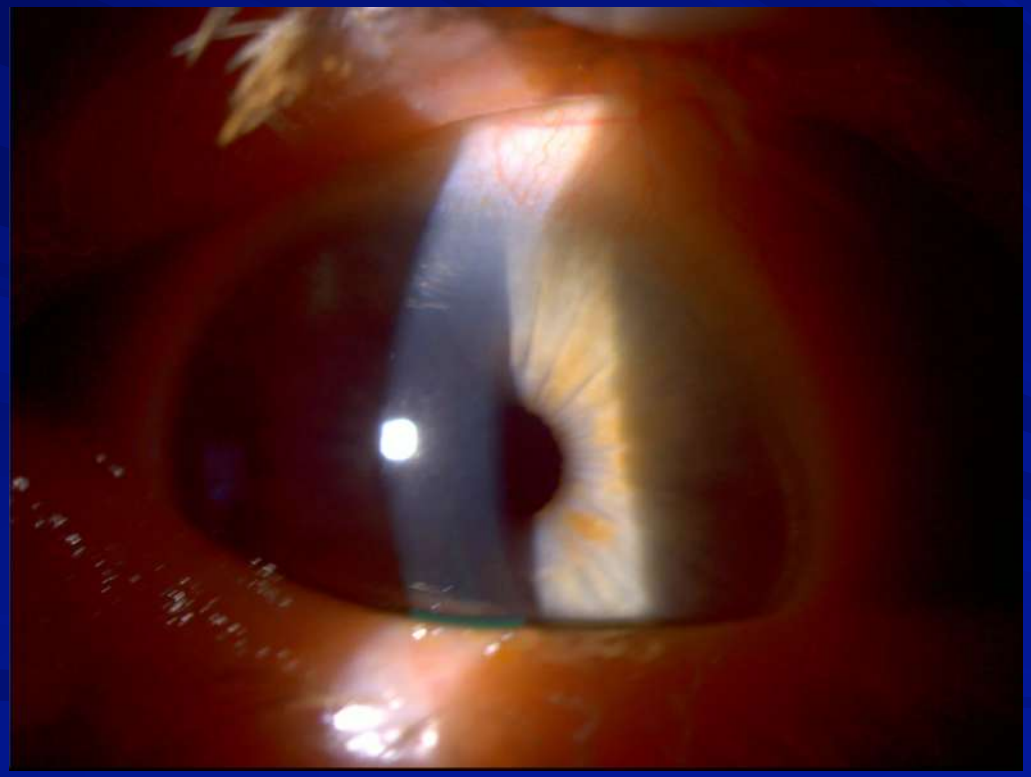



# Corneal Sensitivity Testing

# Cornea Sensitive Testing – Another Patient



# Cornea Sensitive Testing – Yet Another Patient

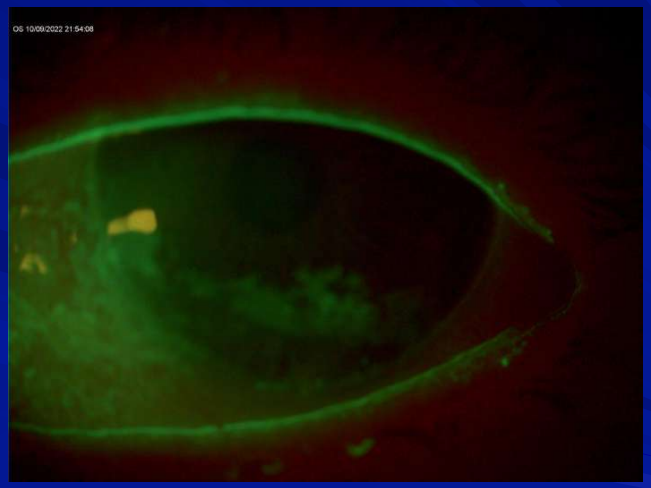


# Oxervate™ (cenegermin-bkbj)

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

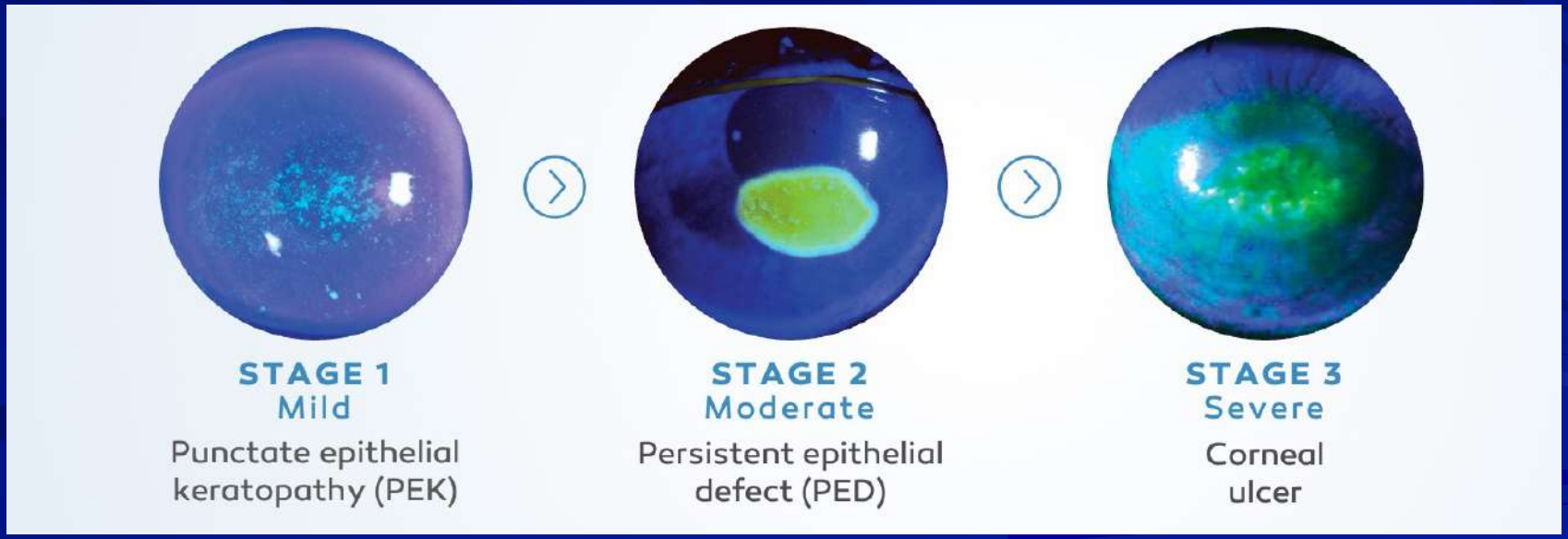
  - Reduced in all quadrants and centrally
  - Absent inferior quadrant, reduced everywhere else

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



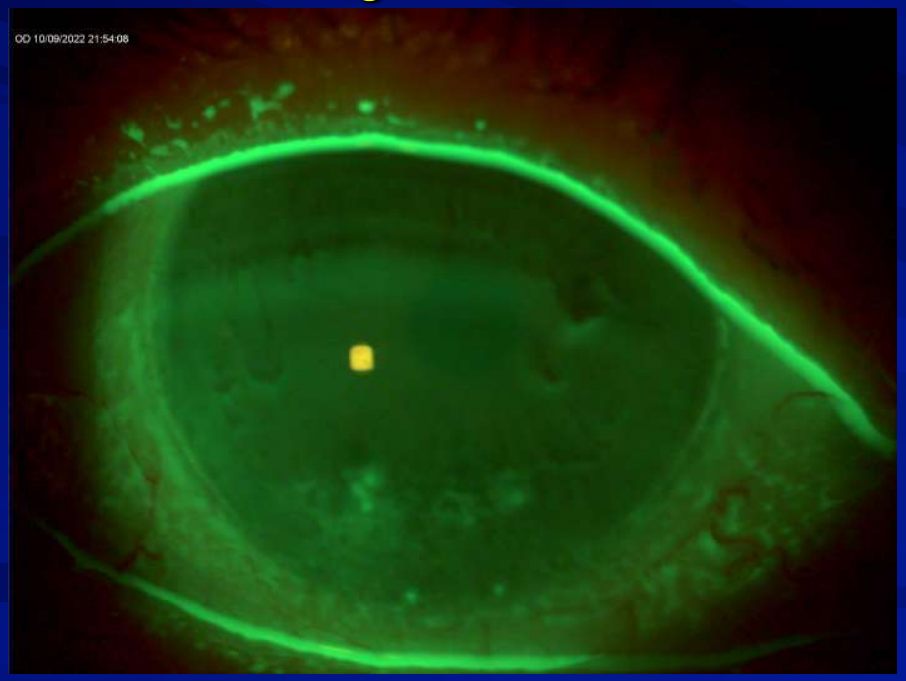
# Neurotrophic Keratitis is a Degenerative Disease

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

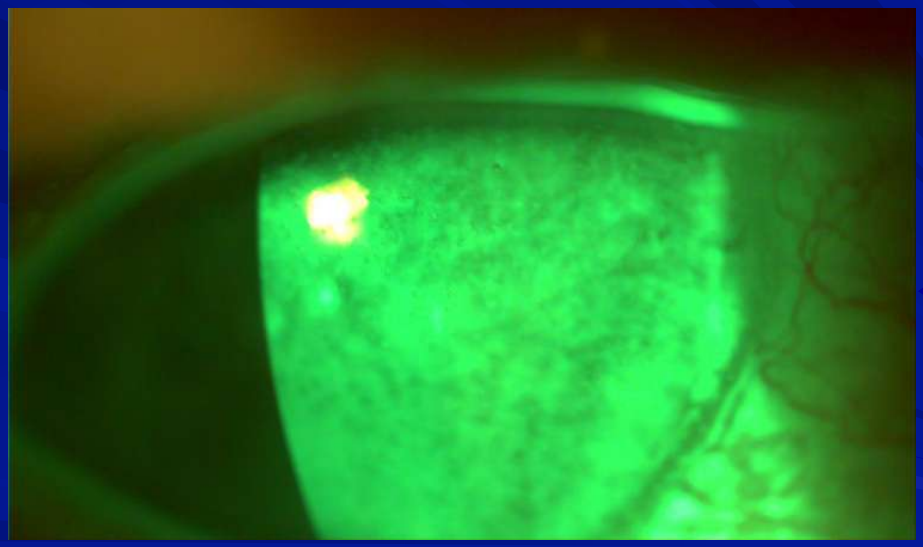


# Mackie Classification

Moderate - Stage 2




Moderate - Stage 2



# Mackie Classification

Moderate - Stage 2

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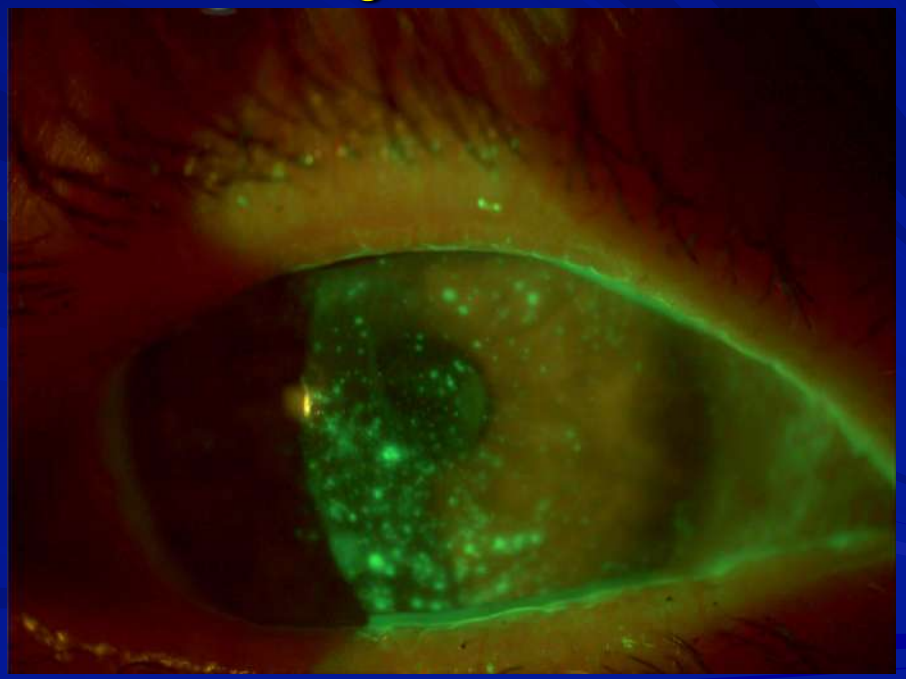
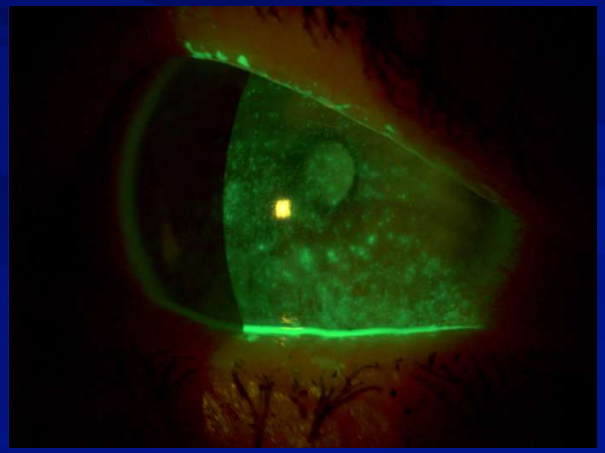


# Resolved



# 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

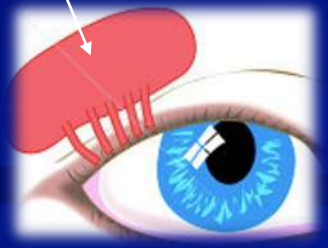
# Dompé Team

# Corneal Homeostasis

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


**Corneal nerves** stimulate blinking and tear production

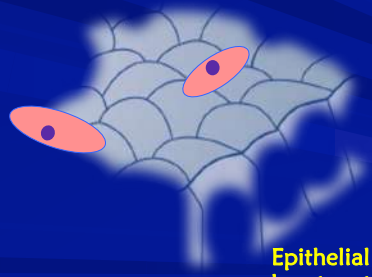
**Tear gland**



**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**

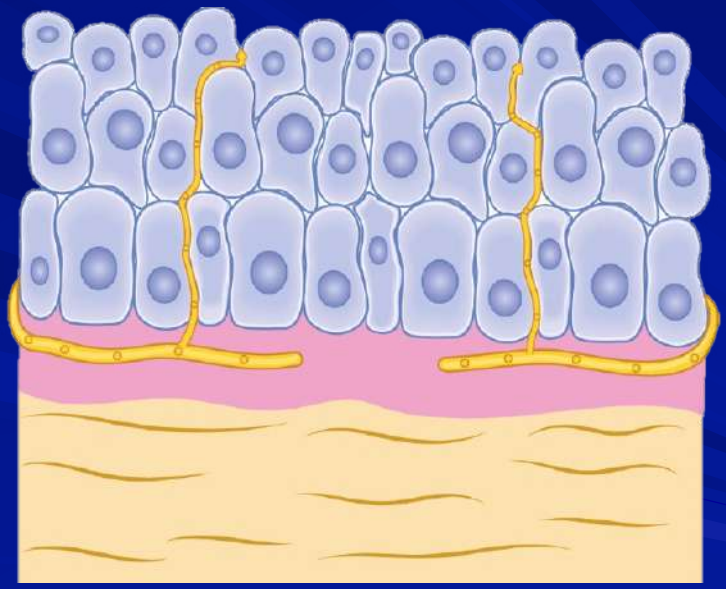
**Neuromediators** provide trophic support to ocular surface tissues (particularly epithelial cells & keratocytes) that:

- Stimulates wound healing
- Maintains anatomic integrity

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

# Pathophysiology of NK[1]

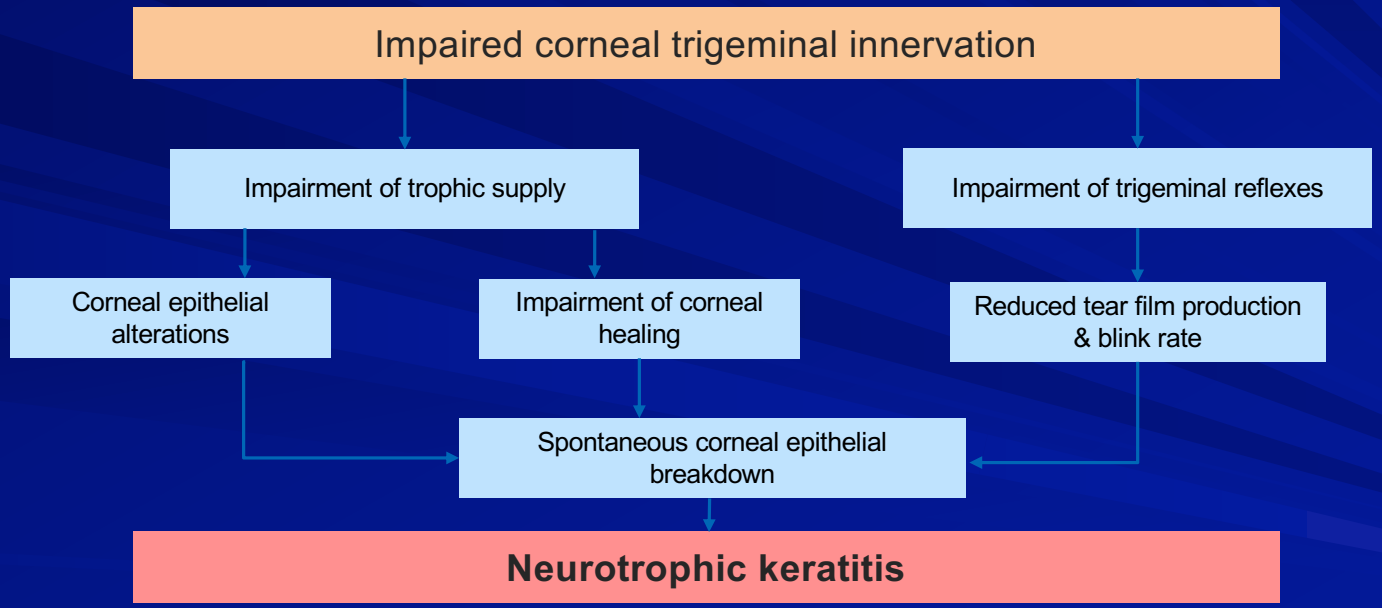
- The loss of corneal sensory innervation via damage to the trigeminal nerve reduces release of neuromediators that provide trophic (nutritional) support to the ocular surface tissues, stimulate wound healing and maintain anatomic integrity
- Impairment of corneal sensitivity also affects tear film production 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

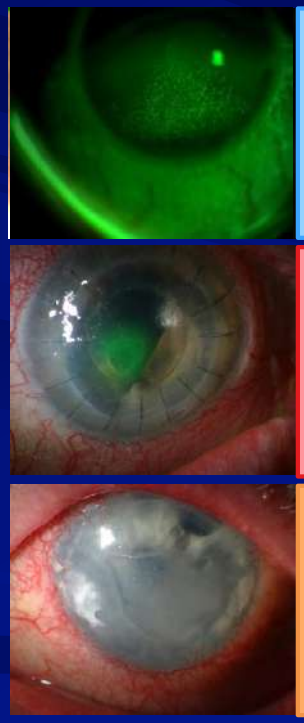
**Systemic**
- Diabetes mellitus
- Leprosy
- Vitamin A deficiency
- Amyloidosis
- Multiple sclerosis

**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



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

**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

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]

Ocular symptoms

**History**

Clinical examination and tests

NK suspected

Test corneal sensitivity

Normal → NK unlikely

Reduced → Further tests required

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]

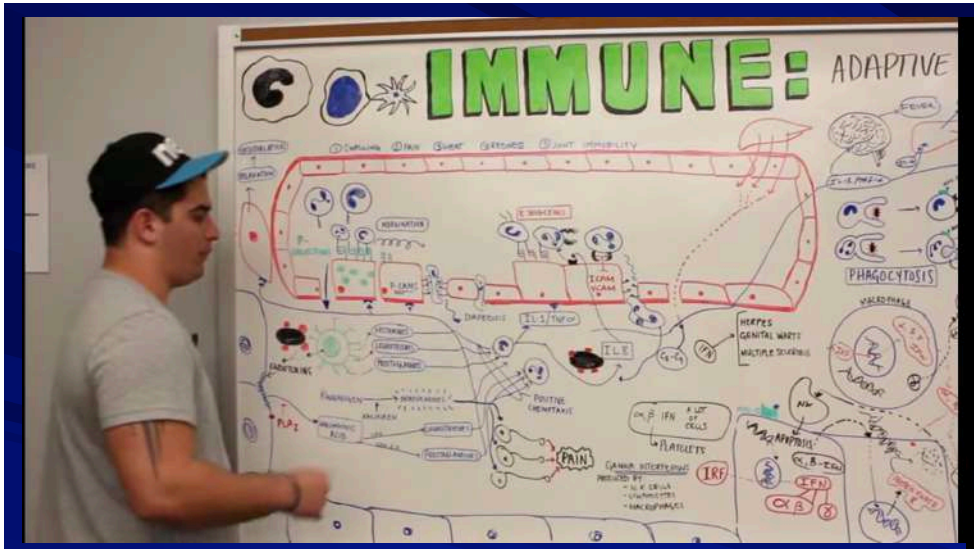
## TEAR SECRETION

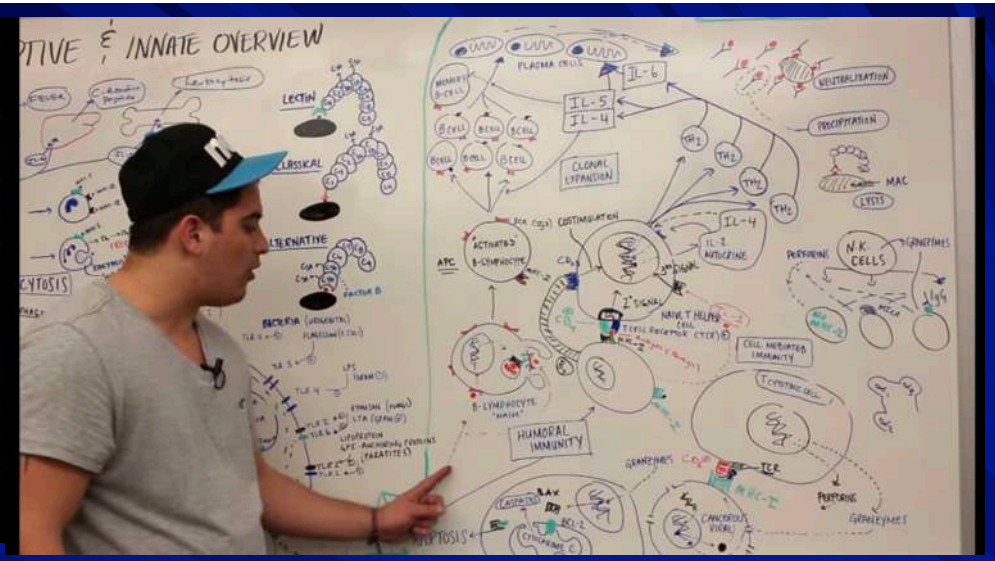
NGF binds receptors on lacrimal glands and promotes sensory-mediated reflex tearing secretion[1,4]

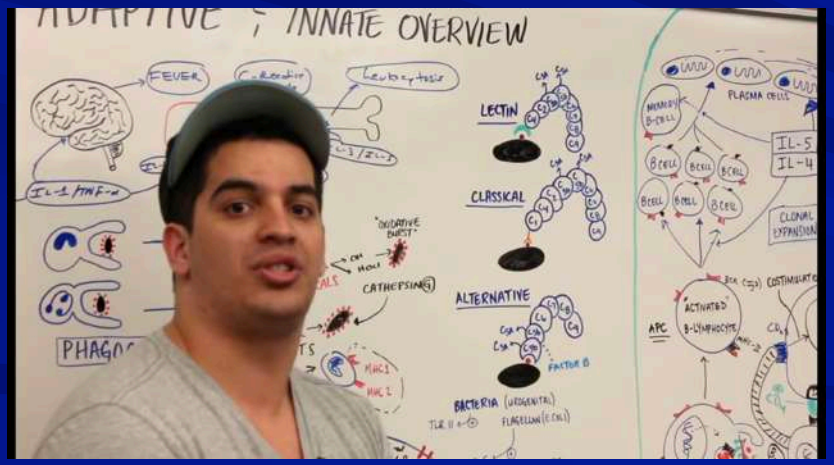
## CELL PROLIFERATION AND DIFFERENTIATION

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:

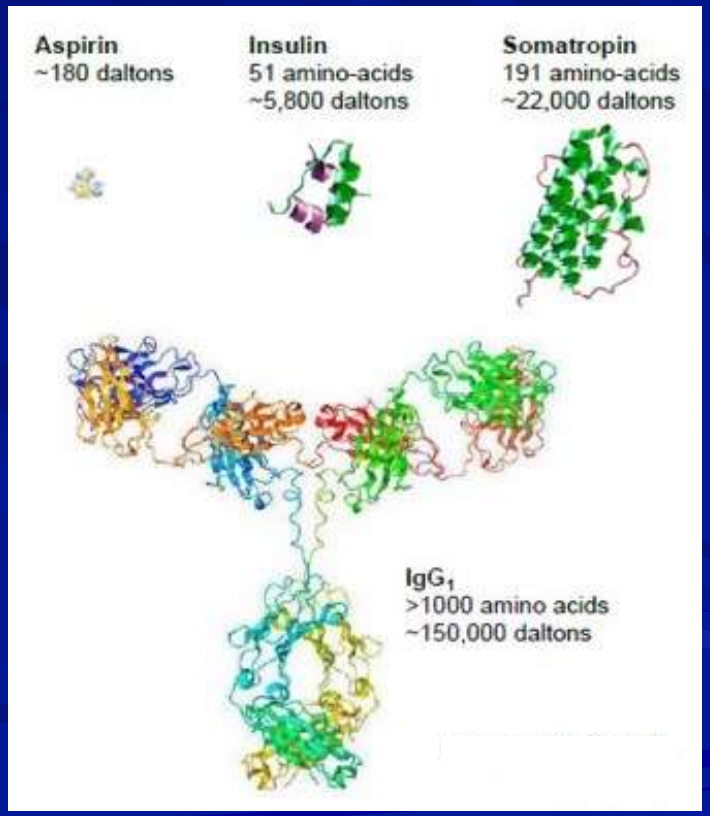
A. Large molecules
B. Small molecules
C. Nano-particles (super small molecules)
D. I don't know, that is why I am here

# Small Molecule Drugs versus Biologics

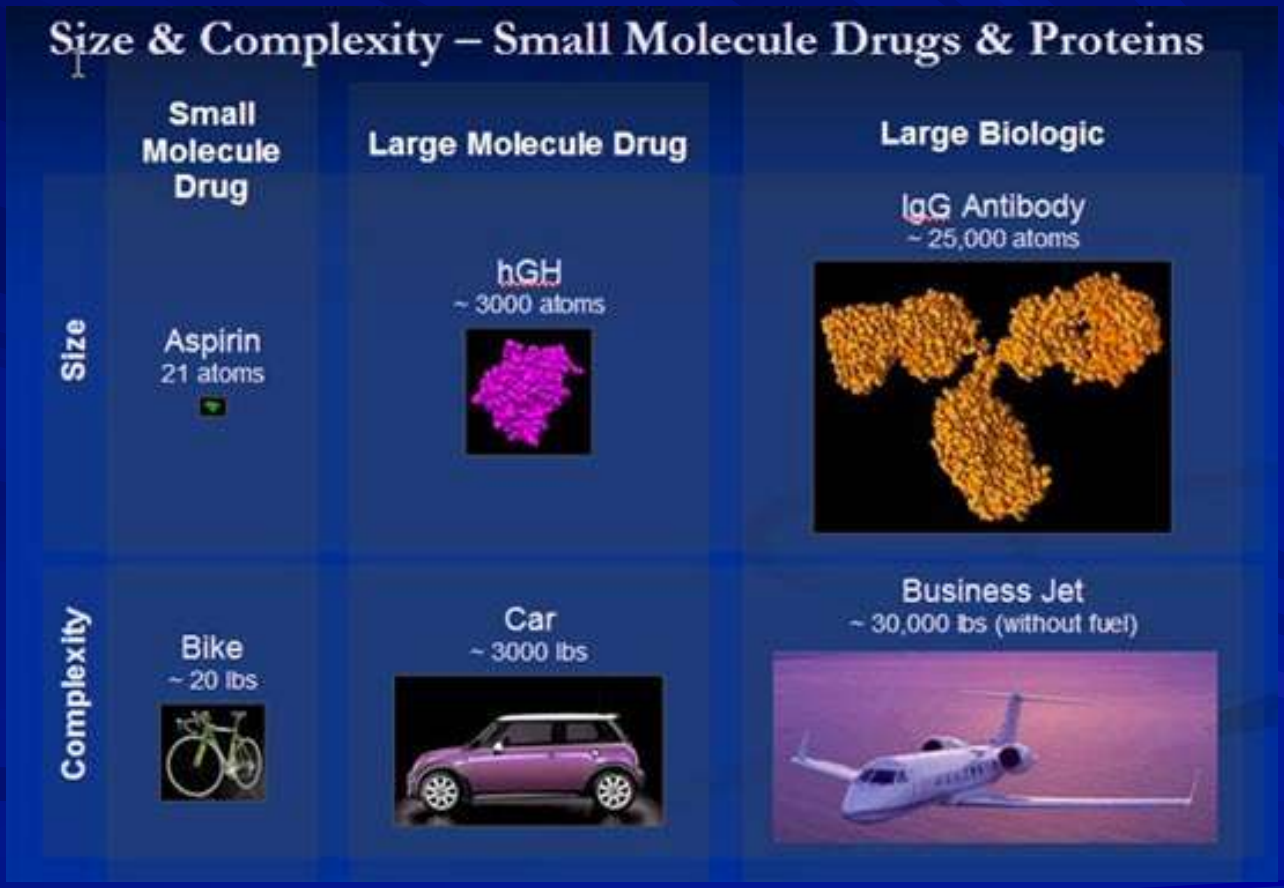
- Small molecule drugs are made by adding and mixing together known chemicals and reagents using a series of controlled and predictable chemical reactions
  - Organic chemistry
  - Inorganic chemistry
- Biologics are made by harvesting the substances produced and secreted by constructed cells
  - Genetic 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)

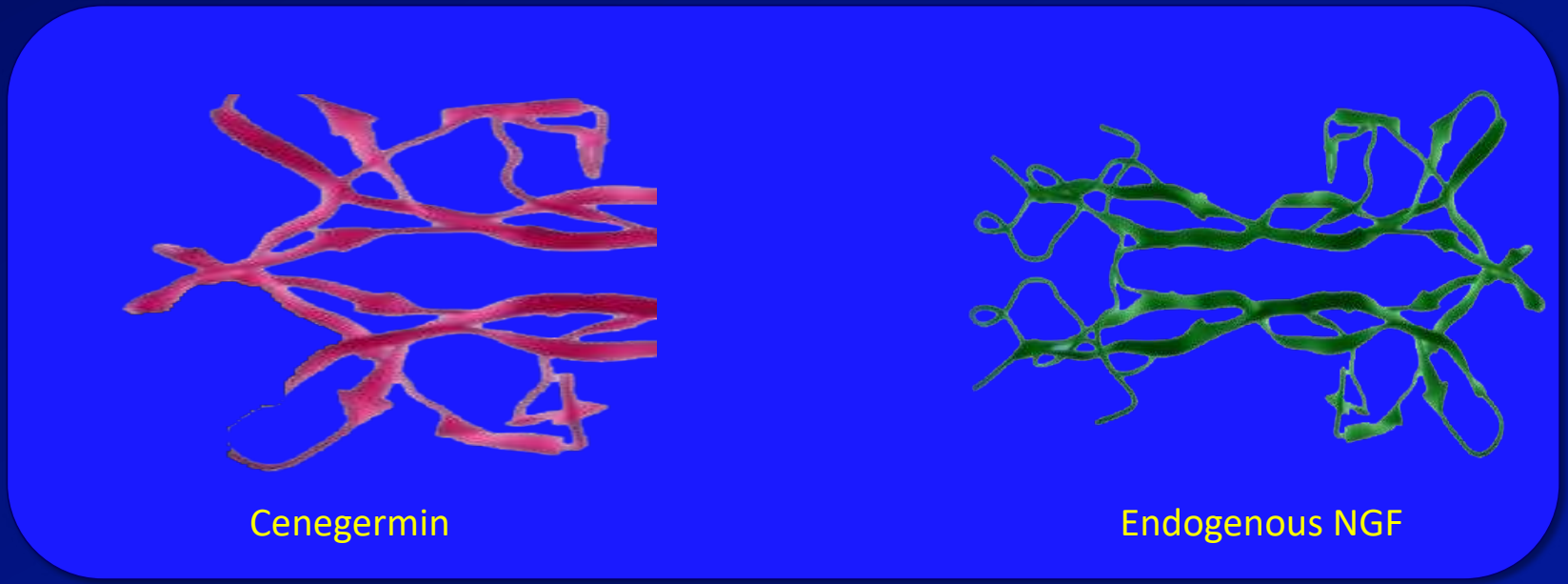
↓

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

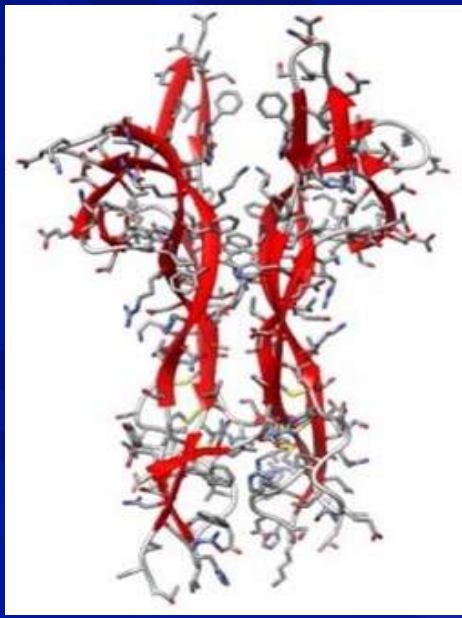



Cenegermin-bkbj, the active ingredient in the FDA-approved OXERVATE™ (cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL), is structurally identical to the human NGF protein found in ocular tissues

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**

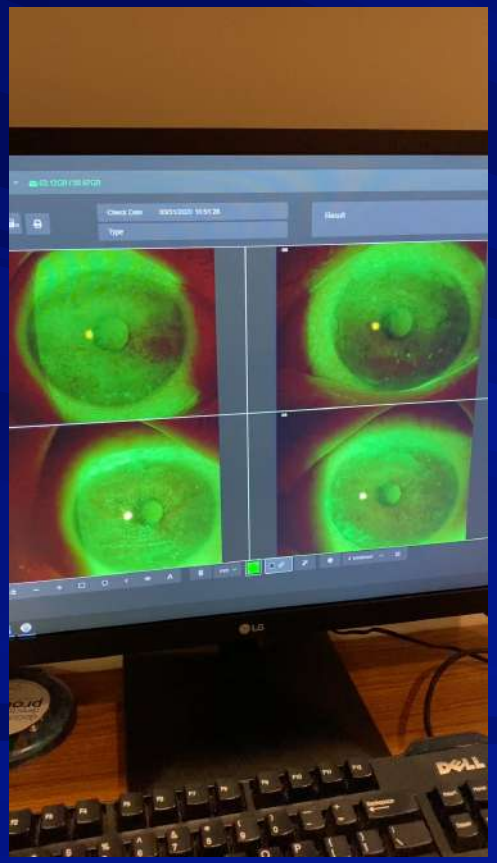
**Apply 6 times daily**

**Continue for 8 weeks**

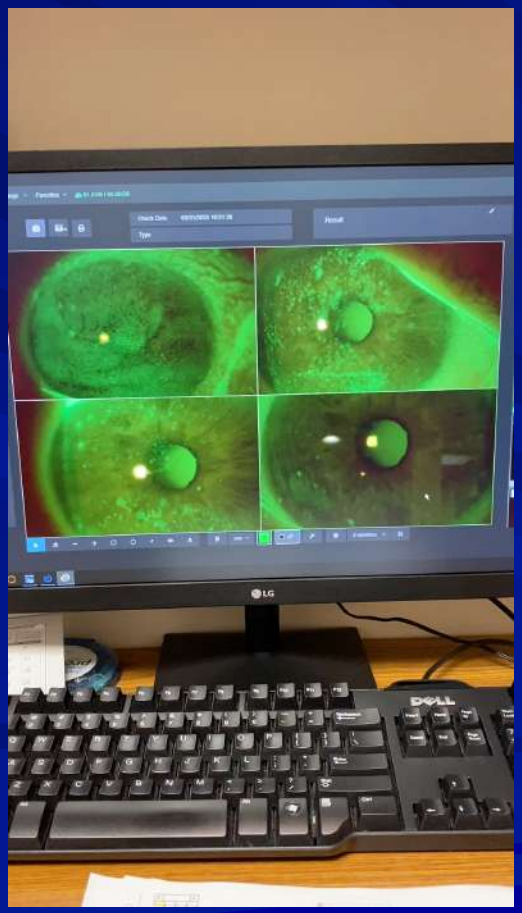
OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.

# Let's Hear From a Patient

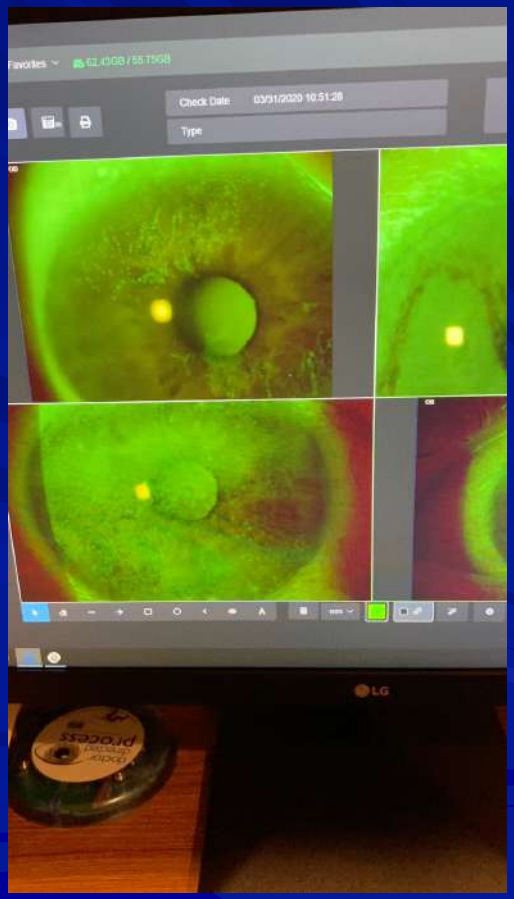
April 7, 2020 - After 1 week



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

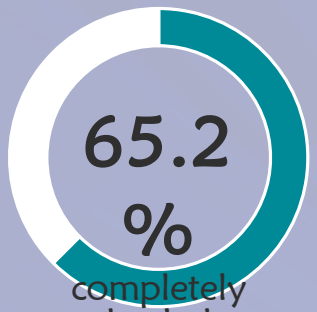
*NCT01756456*


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

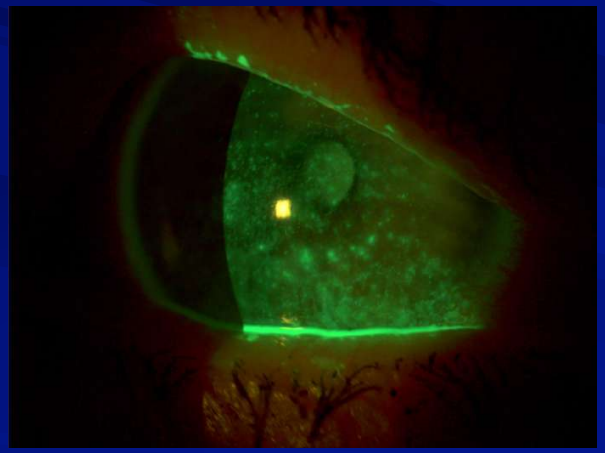
**Safety:** The most common adverse reaction was eye pain following instillation which was reported in approximately 16% of patients. Other adverse reactions occurring in 1-10% of OXERVATE™ patients and more frequently than in the vehicle-treated patients included corneal deposits, foreign body sensation,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



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# Question and Thank You!

# The Non-Healing Cornea Neurotrophic Keratitis

Greg Caldwell, OD, FAAO

Mackinac Island Northern Escape
Optometric Education Consultants

Saturday, August 19, 2023