



**The Non-Healing Cornea
Neurotrophic Keratitis**


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Mid-Winter Getaway
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Disclosures- Greg Caldwell, OD, FAAO
All relevant relationships have been mitigated

- Lectured for: Alcon, B&L, BioTissue, Dompé
- Disclosure: Receive speaker honorarium
- Advisory Board: Dompé, ImmunoGen, Iveric
- Disclosure: Receive participant honorarium
- I have no direct financial or proprietary interest in any companies, products or services mentioned in this presentation
- Disclosure: Non-salaried financial affiliation with Pharmacia
- 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 digging so many aspects of optometry (scientific, clinical, experience, teacher & lecturer). It is refreshing and very informative. Sarah

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Which Eye is More Symptomatic?

Stain without pain!



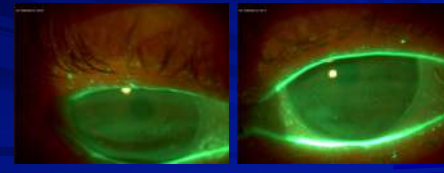
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Before Oxervate™ (cenegermin-bkbj) Treatment



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After Oxervate™ (cenegermin-bkbj) Treatment



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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



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Neurotrophic Keratitis is a Degenerative Disease

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



STAGE 1	STAGE 2	STAGE 3
Mild	Moderate	Severe
Punctate epithelial keratopathy (PEK)	Persistent epithelial defect (PED)	Severe Corneal ulcer

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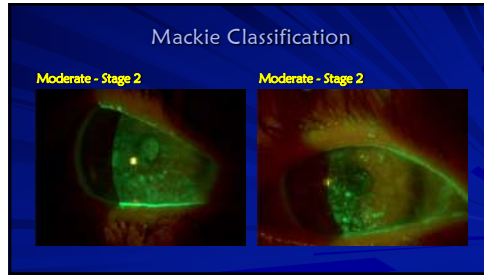
Mackie Classification



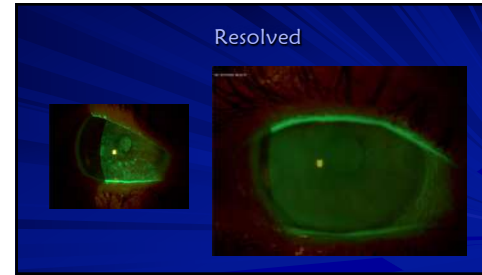
Moderate - Stage 2

Moderate - Stage 2

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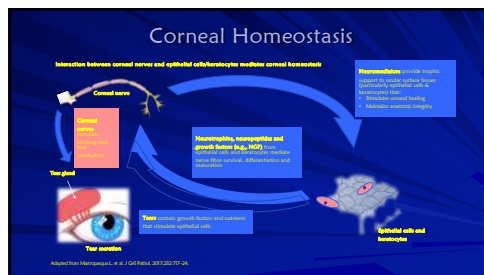
Oxervate™ (cenegermin-bkbj)

- ✓ Approved 2018 (August 28, 2018)
- ✓ Dompé pharmaceutical 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 vial in the fridge – once “actively ready” for use, then it is only stable for 12 hours
- ✓ Contraindications
 - None

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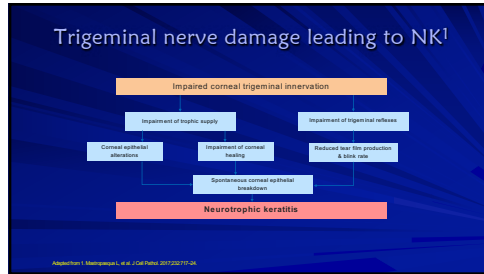
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Pathophysiology of NKI

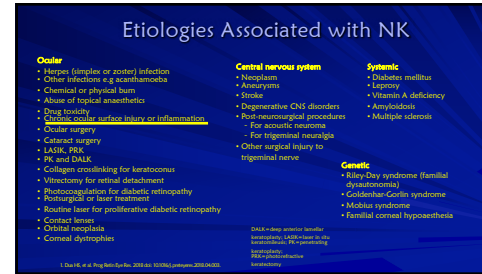
- The loss of corneal sensory innervation via damage to the trigeminal nerve reduces release of neurotrophins that provide trophic (nutritional) support to the ocular surface tissues, stimulate wound healing and maintain anatomical integrity
- Impairment of corneal sensitivity also affects tear film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

The diagram shows a cross-section of the cornea. It highlights the loss of sensory innervation from the trigeminal nerve, which leads to a reduction in neurotrophin release. This results in impaired tear film production and blink rate, ultimately leading to the development of neurotrophic keratitis (NKI). The diagram shows the layers of the cornea and the underlying structures affected by the loss of innervation.

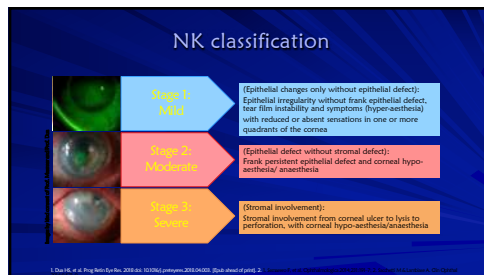
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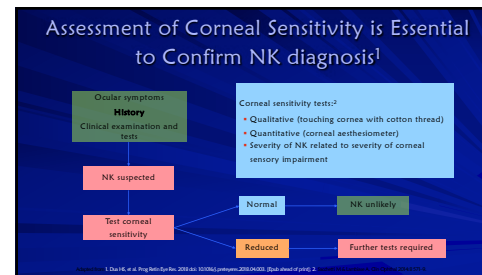
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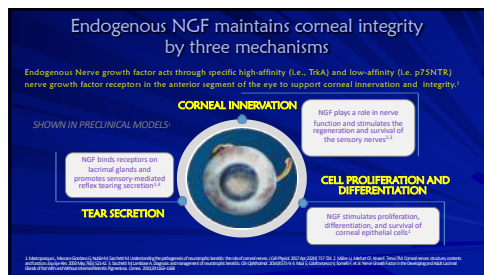
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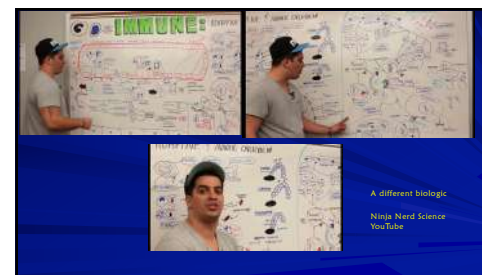
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Biologic Drugs

- ~ 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

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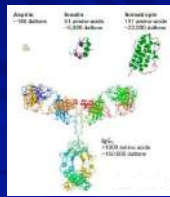
Small Molecule Drugs versus Biologics

- ~ 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 closest manufacturing process of a biologic drug

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Biologic Drugs versus Small Molecule Drugs

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



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Size and Complexity of Biologic Drugs

Size & Complexity – Small Molecule Drugs & Proteins

	Small Molecule Drug	Large Molecule Drug	Large Biologic
Size	Aspirin 180 Daltons	IGG1 150,000 Daltons	IGG Antibody 150,000 Daltons
Complexity	Bike 10,000 parts	Car 100,000 parts	Business Jet 10,000,000 parts

<https://associationoptometriceducation.com/biologics-and-the-biotech-debate>

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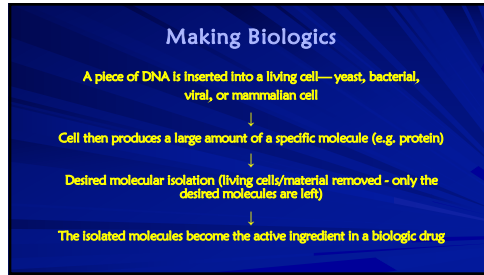


Question?

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

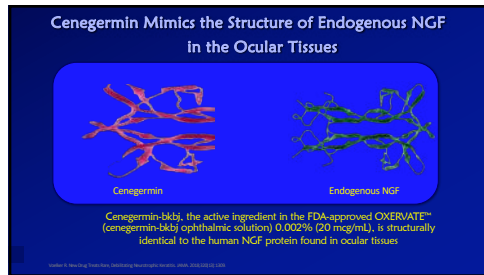
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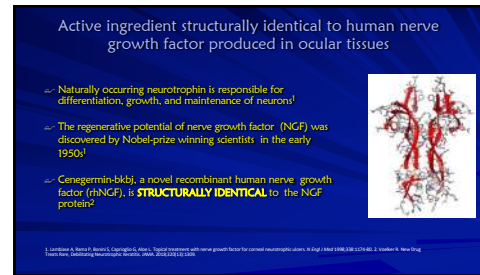
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OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% Weekly Device Kit

- 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.

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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)

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Every 2 hours

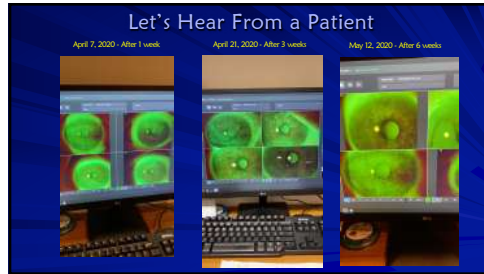
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Apply 6 times daily

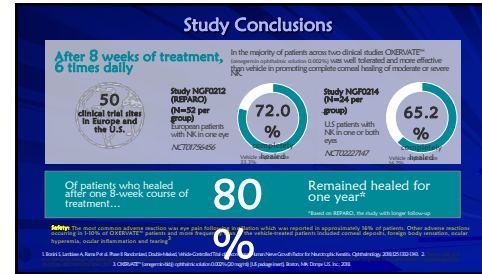
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Continue for 8 weeks

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OXERVATE™ (cenegermin-bkjb)

- 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-bkjb onto the corneal lesion
 - Lenses may be reinserted 15 minutes after administration.

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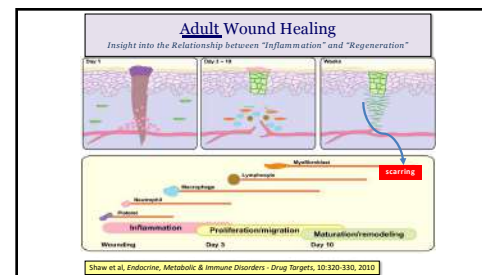


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Amniotic Membrane

Alternative or
While waiting for Oxervate

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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 fits
 - * Anti-Seed Biotech/Bythe Medical
 - * Eclipse- Ophthalmologix
 - Single and dual layer
 - 45 microns of amnion, increased tensile strength

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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

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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

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PROKERA: Original amniotic membrane (patented mylar®) - The most commonly used - Ideal for IOL with keratitis - Alternative ring for improved outcomes

PROKERA Slim: Disposable IOL for keratitis indications such as severe DED, DEDS, Chronic Keratitis, D. Regener's

PROKERA PLUS: Disposable IOL for keratitis indications such as severe DED, DEDS, Chronic Keratitis, D. Regener's

PROKERA Lense: Same design as Plus, but with aperture for improved vision during treatment

PROKERA Lense: Layer of IOL with a unique hydrogel properties such as Proteoglycan, GAG, and HA

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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

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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)
 - * Proteoglycan

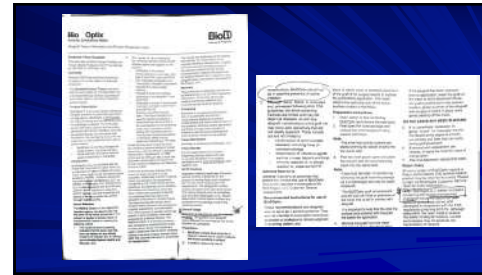
Other proteins of great effectiveness are:

- * Endothelial Cell Adhesion
- * Matrix Metalloproteinase
- * Endothelial Cell Adhesion

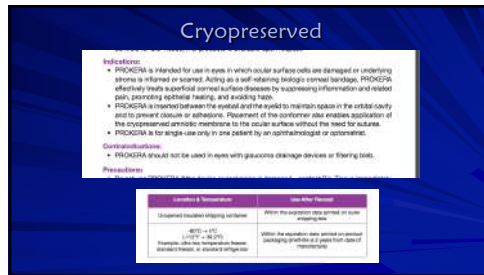
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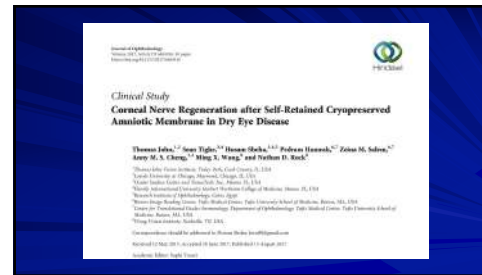
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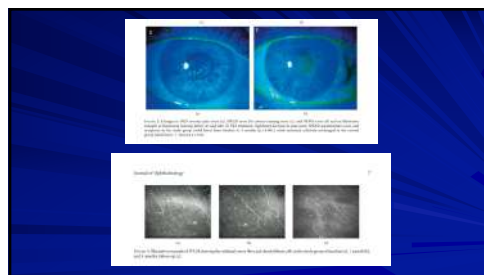
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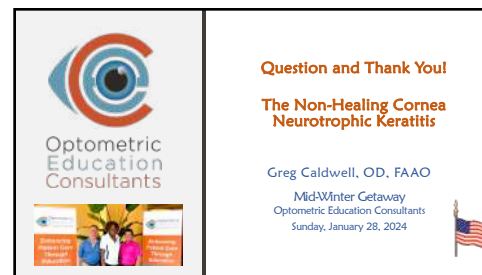
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