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Gene Therapy for Inherited Retinal Disease

Ohio Ophthalmological Society

February 24th, 2024

Thomas A. Mendel, MD PhD
Assistant Professor of Ophthalmology

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Grant Funding:

- Knights Templar Career Starter Grant
- Ohio Lion's Eye
- Center for Clinical and Translational Science Path 2 K Award
- NIH NEI Loan Repayment Program Awardee
- Research to Prevent Blindness New Chair Challenge Grant
- Biomarin research funding for enzyme replacement OCT reads

Center for Clinical and Translational Sciences

Ohio Lions Eye Research Foundation, Inc.
Research Today . . . Vision Tomorrow

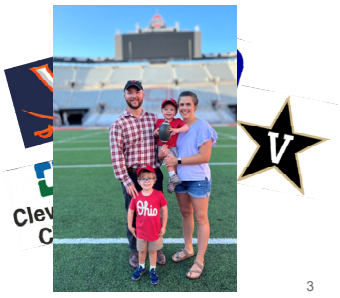
Research to Prevent Blindness

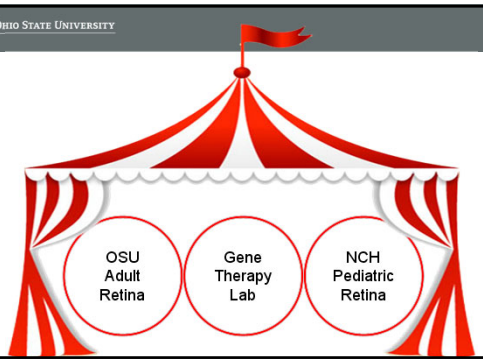
NIH National Eye Institute

"A Masonic Charity"

My Background

- Clinician scientist retina surgeon (pediatric/adult)





Slide 1

1	go to slide master view and add unique titles to all slides. They will not be visible, but will be used by screen readers tOSU uCOM, 1/6/2016

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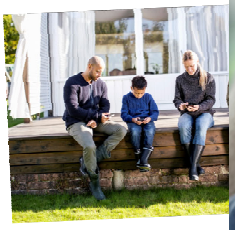
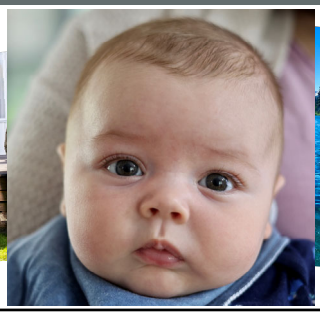
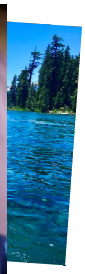
Why vision matters…







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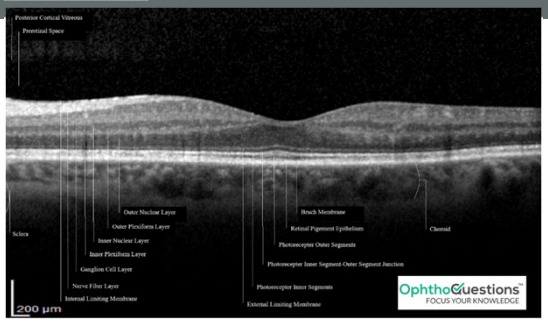

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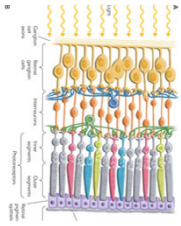
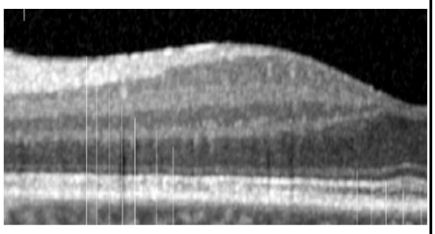
Review of Retinal Architecture





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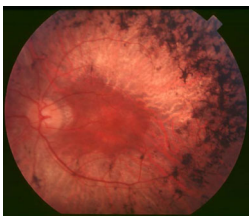
Inherited Retinal Degeneration Basics

- Usually bilateral
- Often progressive
- Over 200 different retinal degenerations identified and growing
- Sometimes an inflammatory component
- Can be thought of as peripheral, macular, vitreous
- Can be associated with systemic diseases (e.g. if a ciliopathy)



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Macular Dystrophies

- Stargardt Disease
  - Most common juvenile macular dystrophy and common cause of central vision loss in adults younger than 50 years
  - Majority are autosomal recessive
  - Vision ranges from 20/50 – 20/200
  - *ABCA4* gene, which encodes ATP binding cassette transporter in rod outer segments.
    - Also *STGD4, ELOVL4, PRPH2* as well

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Macular Dystrophies

- Stargardt Disease
  - Clinical features
    - Yellow “pisciform flecs” at level of RPE
    - Called “fundus flavimaculatus”
    - Silent “dark choroid” on fluorescein angiography
- Do NOT give them vitamin A supplementation

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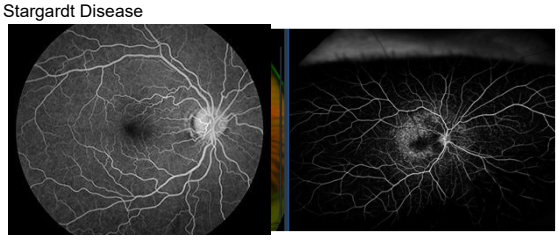
Macular Dystrophies

- Stargardt Disease



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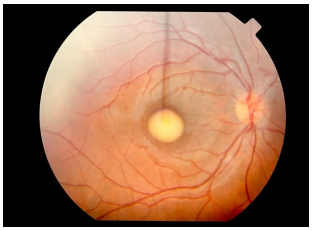
Macular Dystrophies

- Best Vitelliform Dystrophy
  - Autosomal dominant *BEST1* on chromosome 11q13
    - *(or VMD2)*
  - Bestrophin localizes to basolateral membrane and is Cl- channel
  - So lipofuscin builds up b/c of faulty pump
  - Egg yolk like “vitelliform” lesion



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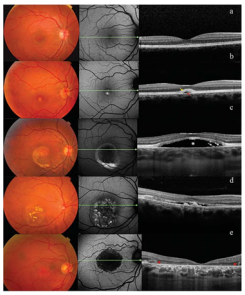
Macular Dystrophies

- Best Vitelliform Dystrophy
  - Progression from egg yolk to scrambled egg
  - Characteristic ERG is normal with abnormal EOG



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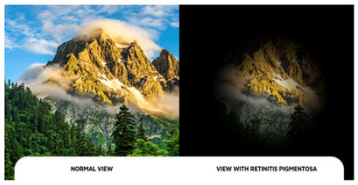
Peripheral Diseases

- Retinitis Pigmentosa
  - >100 different genetic mutations grouped under this name
  - 2 large groups (primary and secondary)
    - Primary RP – diseases of photoreceptors
    - Secondary is from mutation associated with other organ disease
  - Many types of inheritance
    - Auto-dominant 10-20% of the time
    - Auto-recessive 20% of cases
    - X-linked is 10% in US and 25% in England
    - At least 40% *have no family history*



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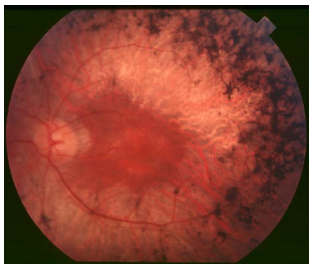
Peripheral Diseases

- Retinitis Pigmentosa
  - Clinical features
    - Bone spicules
    - Waxy pallor of disc
    - Arteriolar narrowing



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Peripheral Diseases

- Leber's Congenital Amaurosis
  - Mutation that affects the retinal pigment epithelium
  - Main role is to replenish cis-retinal for use by photoreceptors
  - Genetics
    - 3 autosomal dominant and 18 recessive mutations
    - Severely reduced vision from birth
    - 20/200 – to NLP (no light perception)
  - Most have normal intelligence
  - Undetectable ERG

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Peripheral Diseases

- Leber's Congenital Amaurosis
  - Clinical features
    - Bone spicules
    - Arteriolar narrowing
    - Choroidal show

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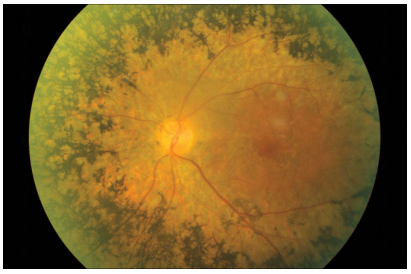

Retinitis Pigmentosa

1. Peripheral pigmentation "bone spicules"
2. Optic nerve "waxy pallor"
3. Vessel attenuation

Lee H, Lotery A. Gene therapy for RPE65-mediated inherited retinal dystrophy completes phase 3. The Lancet. 2017/08/26/ 2017;390(10097):823-824. doi:https://doi.org/10.1016/S0140-6736(17)31622-7

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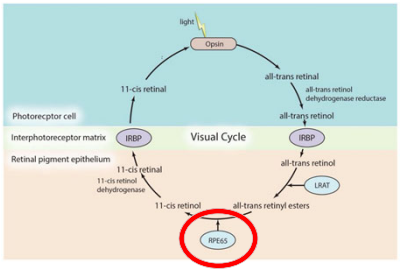

Chiu W, Lin TY, Chang YC, et al. An Update on Gene Therapy for Inherited Retinal Dystrophy: Experience in Leber Congenital Amaurosis Clinical Trials. *Int J Mol Sci*. 2021;22(9):4534. Published 2021 Apr 26. doi:10.3390/ijms22094534

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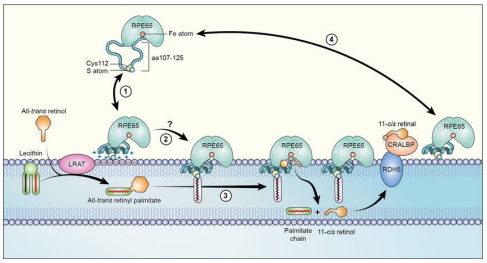

Uppal, Sheetal & Liu, Tingting & Galvan, Emily & Gomez, Fatima & Tittley, Tishina & Poliakov, Eugenia & Gentleman, Susan & Redmond, Thomas. (2022). An inducible amphipathic α-helix mediates subcellular targeting and membrane binding of RPE65. Life Science Alliance. 6. e202201546. 10.26508/lsa.202201546.

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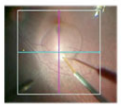
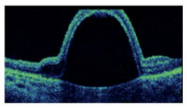
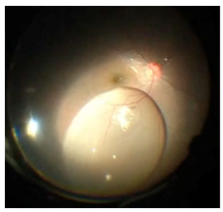
Subretinal Delivery
(e.g. Luxturna for LCA)







Surgical Video

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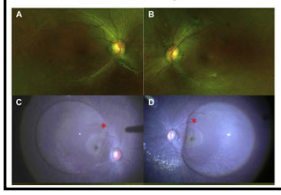
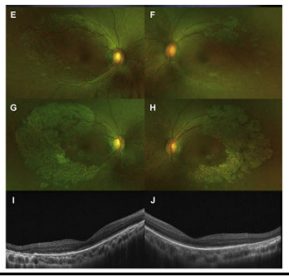
Perifoveal Chorioretinal Atrophy after Subretinal Voretigene Neparvovec-rzyl for RPE65-Mediated Leber Congenital Amaurosis

William S. Gange, MD,[1,2] Robert A. Sisk, MD,[1,2,3] Capri G. Bonki, MD, PhD,[1] Thomas C. Lee, MD,[1,2] Margaret Hennigan, MPH,[1] Hillary Schwartz, MS,[1] Mark Breehen, MD,[1,2] Jesse D. Sengillo, MD,[1] Carlos Mendoza, MD,[1] Audrie M. Bertocci, MD,[1] Aaron Nagel, MD, PhD[1,2]





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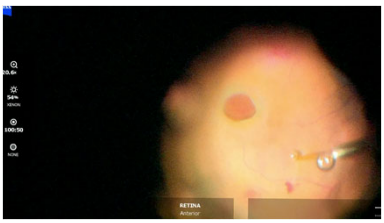
Challenges include:
- Retinal detachment control
- Inflammation
- Atrophy

WHAT ABOUT OTHER GENETIC DISEASES?!?



In a two week period, seeing patients only 2 days per week, I saw patients with the following mutations: *USH2A* (2 patients), *CRB1, NR2E3, SLC29A3, TULP1, PRPH2, AHI1, ABCA4* (2 patients), *OCA2, CDHR1, RPGR, CHM, RLBP1, EYS, COL2A1,* and *PDE6C*

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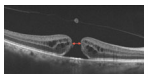
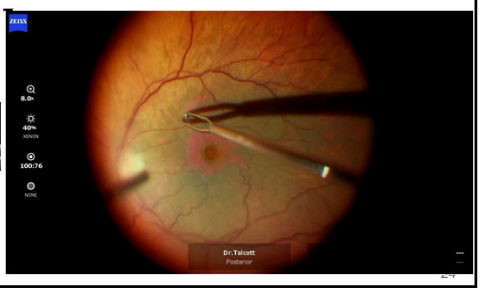
Retina Surgery
Macular hole





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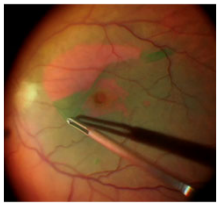
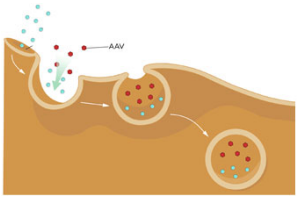
Remove the Barrier to the Retina – the Inner Limiting Membrane



Add **Incorporation Factors** to the AAV gene therapy to induce cellular uptake of extracelluar material.



Gene Agnostic Approach

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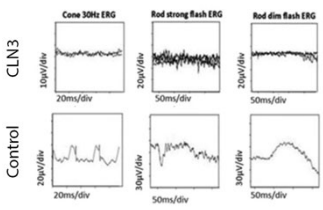
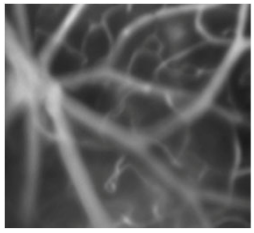
Retinal Function and Inflammation





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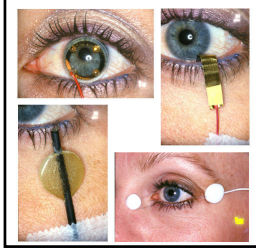
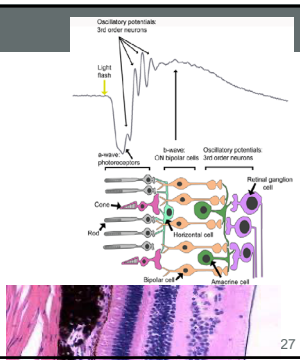
Other Techniques

ERG – (Electroretinography)





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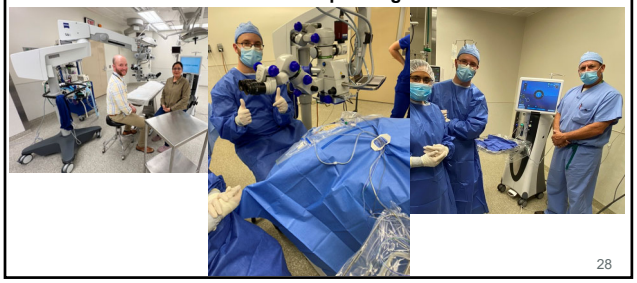
Let's Build and Operating Room



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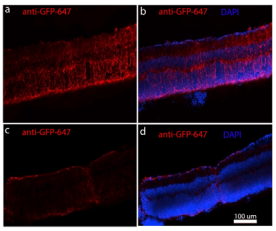
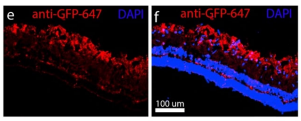
And Build a Veterinary Eye Clinic

Mouse Retinal Explant



Pig Live Surgery



AAV + Incorporation Factors demonstrates protein expression throughout retina

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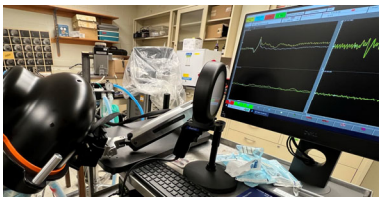

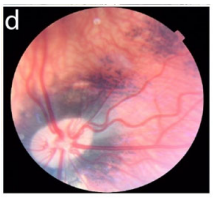

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Takes a great team!

Angie Kondziela

Sarah Yoest

Julie Racine

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