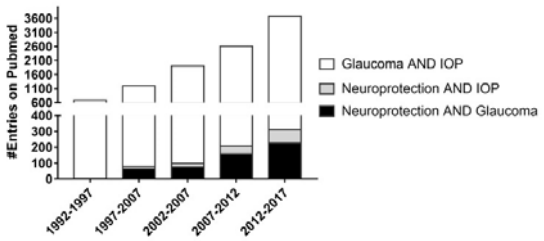
Neuroprotection in Glaucoma

Neuroprotection research is rapidly advancing

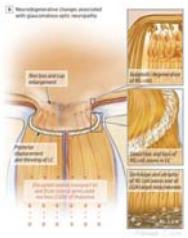


Current state

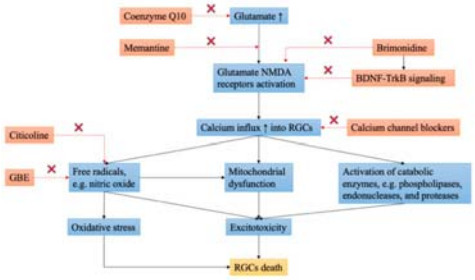
No fundamental breakthroughs for over 100 years in glaucoma

- All available therapies lower intraocular pressure (IOP)
- Despite IOP lowering, patients progress to irreversible loss of visual field

No therapies focus on the underlying biology: damage to retinal ganglion cells (RGCs)



Multiple points identified for neuroprotection



Kuo and Lui. J Pers Med. 2022 Nov; 12(11): 1884.

Damage from Glaucoma is multifactorial IOP lowering is not enough

Damage is irreversible
IOP lowering is useful but
4.4% of medicated patients develop Glaucoma despite 225 IOP lowering Ocualr Hypertension Treatment study
45% progress despite a 25% reduction in IOP in the early Manifest Glaucoma trial
12% progress with IOP of 10.6 in the normal tension glaucoma trail.
Therapeutic interventions are targeted at multiple places in the known pathways to protect from damage.

Multiple Retinal Neuroprotection Indications

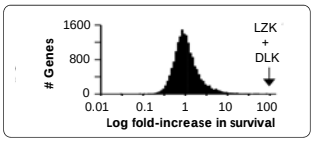
Images: Eyewiki.org for RP, CRVO, Glaucoma, LHON, AAO for NAION

- **Retinitis Pigmentosa**
  - USA prevalence: 100k patients[1]; mid-life vision loss
  - No current therapy for >95% of patients
- **Leber's Hereditary Optic Neuropathy (LHON)**
  - USA prevalence: <2000
  - Idebenone approved in EU, provides incomplete protection
- **Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION)**
  - USA incidence: ~5000 events/year[2]
  - No therapy available
- **Glaucoma**
  - USA prevalence: 120k patients with significant blindness[2]
  - Therapies focus on intraocular pressure not neuroprotection
- **Retinal Vein Occlusion (Ischemic CRVO/BRVO)**
  - USA prevalence: >100k patients[4]
  - Current therapies focus on neovascularization, not neuroprotection

References for this slide are in PowerPoint Notes due to length

Whole-Genome Screen Identifies Critical Role for DLK/LZK

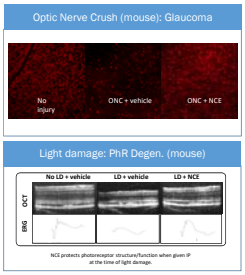
- Conducted by Drs. Don Zack and Derek Welsbie (JHU)
- siRNA **whole mouse genome screen** identified genes that are **causally-involved** in retinal ganglion cell (RGC) death
- DLK/LZK were **#1 out ~20,000**



Inhibition of DLK in the setting of LZK disruption was the **single most robust** neuroprotective intervention. Welsbie et al., *Neuron*, 2017.

PRECLINICAL EFFICACY IN VIVO IN OPHTHALMIC DISEASE MODELS

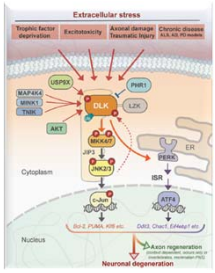
- Preclinical POC in >8 distinct models, including 3 models of glaucoma
  - Strong efficacy in NHP Glaucoma model*
  - Multiple cell types: RGCs, Photoreceptors, and others
- Multiple disease applications
- Multiple APIs in patent; can leverage distinct, novel APIs in different indications



DLK / LZK Mechanism of Action

DLK/LZK mediate neuronal injury signaling

- Triggers cell death; DLK/LZK inhibition is **robustly protective**
- Applies across a **broad range of injury types**, neuron types and animal species
- **DLK/LZK inhibition** reduces deleterious injury-induced changes in gene expression; **maintains function**
- **DLK pathway is highly evolutionarily conserved**



Siu et al., *J Med Chem*, 2018

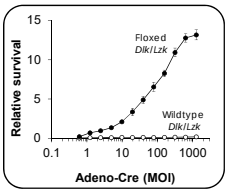
Preclinical Testing: In Vitro Retinal Neurons

Mouse primary RGCs:

- Axotomy model
- Validated with cre/lox KO, siRNA, small molecule inhibitors

Human stem cell-derived RGCs:

- Models of cell death: microtubule disruption, ER stress, oxidative stress, mitochondrial dysfunction
- Validated with CRISPR KO, siRNAs, small molecule inhibitors

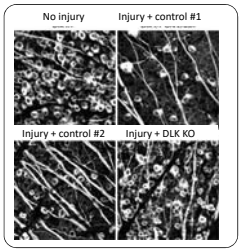


DLK/LZK knockout robustly increases mouse RGC survival 72 hours after injury. Welsbie et al., *Neuron*, 2017

DLK/LZK INHIBITION HOLDS PROMISE IN ALS, NEUROPATHIC PAIN, PARKINSON'S, ALZHEIMER'S, TRAUMATIC BRAIN INJURY

- DLK/LZK Pathway is active in several major CNS diseases
- Local delivery of inhibitors may protect from degenerative diseases & neuropathic pain

Preclinical Testing: In Vivo RGC Injury



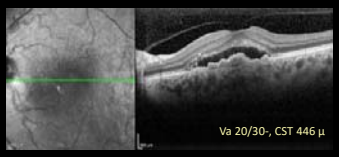
DLK knockout improves RGC survival 2 weeks after optic nerve crush (ONC). Welsbie et al., *PNAS*, 2013.

Hot Topics in Retina

Christina Y. Weng, MD, MBA
Professor of Ophthalmology
Fellowship Program Director, Vitreoretinal Diseases & Surgery
Baylor College of Medicine, Houston, TX
New Orleans Academy of Ophthalmology 72nd Annual Symposium
February 12, 2023

Patient example

- 71 y/o F with new dx of wet AMD OS; Va 20/30-
- OD intermediate dry AMD; Va OD 20/20



- Bevacizumab
- Ranibizumab
- Aflibercept
- Brolucizumab
- Faricimab
- Ranibizumab-nuna
- Ranibizumab-eqrn
- (PDS)

Disclosures

- Alcon, Allergan/AbbVie, Alimera Sciences, REGENXBIO, Novartis, Regeneron, DORC, Genentech, Opthea (consultant)
- DRCR Retina Network, Alimera Sciences, AGTC (research)
- Springer Publishers (royalties)

Brolucizumab

- Brolucizumab is a 26 kDa humanized single-chain antibody fragment with high molar dose that targets all VEGF-A isoforms
  - FDA-approved in October 2019 for nAMD
- Brolucizumab non-inferior to AFL q8 in BCVA and dried better on OCT[1]

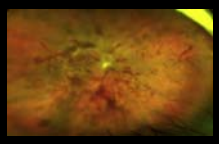

[2]

[1]Dugel PU, et al. *Ophthalmology*. 2020;127(1):72-84.
[2]https://retinatoday.com/articles/2019-may-june/emerging-treatments-for-neovascular-amd?c4src=article:sidebar.

Hot Topic #1: Wet AMD therapeutics

Brolucizumab (cont.)

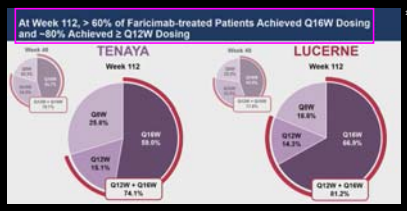
- Durability[1]:
  - Approximately half of eyes receiving brolucizumab maintained on q12 week dosing through 1 year
- Safety:
  - Post-marketing reports of intraocular inflammation (IOI), retinal vasculitis (RV), and vascular occlusive events (RO)
    - In HAWK/HARRIER, 4.6% had IOI of any form; 3.3% had IOI + RV; 2.1% had IOI + RV + RO[2]
      - Risk of developing IOI + losing ≥15 letters was 0.7%
    - Etiology remains incompletely understood
  - Phase 3 studies MERLIN (NVAMD), RAVEN/RAPTOR (MEfRVO) halted


[3]

[1]Dugel PU, et al. *Ophthalmology*. 2020;127(1):72-84.
[2]www.aao.org.
[3]Baumal CR, et al. *Ophthalmology*. 2020;127(10):1345-59.

Faricimab

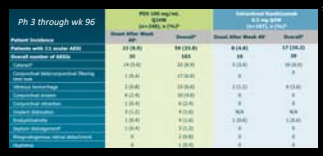
- Faricimab is a bispecific molecule that targets VEGF-A and Ang-2
  - FDA-approved for the treatment of wet AMD & DME in January 2022



[1]Courtesy of Genentech.

PDS adverse events

- Endophthalmitis occurred in 4 (1.6%) PDS patients and 1 (0.6%) monthly ranibizumab patient—led to FDA boxed warning
- Voluntary recall of PDS in October 2022 due to failure to meet internal standards in testing prompted by post-approval septum dislodgement



[1]Courtesy of Genentech.
[2]www.asrs.org.

Biosimilars

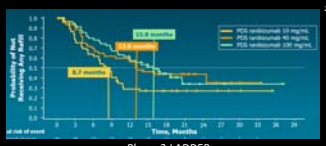
- A biosimilar is a molecule considered highly similar (not identical) to the originator biologic
  - Typically smaller trials with shorter time to primary endpoints
  - Often offer a modest discount relative to reference product
- Ranibizumab-nuna
- Ranibizumab-eqrn
- Once bioequivalence is shown in one indication, can apply for extrapolation which extends indications to others held by the reference product
- If biosimilar is granted interchangeability by the FDA, the drug can be substituted for the reference product at the pharmacy level in states where this is permitted

Therapeutics of tomorrow (investigational)

- High-dose aflibercept
- OPT-302
- KSI-301
- Gene therapy
  - RGX-314
  - ADVM-022
  - HMR59
  - 4D-150
- TKIs
  - OTX-TKI
  - EYP-1901
  - GB-102

Port delivery system (PDS) with ranibizumab

- Surgically implanted device provides continuous release of concentrated ranibizumab
- ~95% of pts did not require supplemental treatment before mandated refill-exchange in Phase 3 ARCHWAY at 96-wk timepoint[1]



Phase 2 LADDER

[1]Holekamp NM, et al. *Ophthalmology*. 2022 Mar;129(3):295-307.
[2]Campochiaro PA, et al. *Ophthalmology*. 2019 Aug;126(8):1141-54.

VEGF inhibitors (investigational)

High-dose aflibercept
- 4X dose (8 mg/0.7cc) of standard aflibercept has shown positive signals in Phase 3 PULSAR study
  - 79%/77% were initiated and maintained on q12-/q16-wk dosing through wk 48
  - Also being studied for DME in Phase 3 PHOTON study

OPT-302
- OPT-302 blocks VEGF-C and VEGF-D
  - OPT-302 (2 mg) + RAN gained 3.4 letters MORE than RAN monotherapy at wk 24
  - Phase 3 ShORe/COAST studies ongoing

KSI-301
- KSI-301 (tarcocimab tedromer) is an anti-VEGF-A mounted on an antibody conjugate (ABC) platform
  - Phase 3 DAZZLE failed to meet primary endpoint
  - Being studied in a q4-wk study called DAYLIGHT
  - Also being studied in Phase 3 programs for DME, DR, RVO

Gene therapies (investigational)

RGX-314

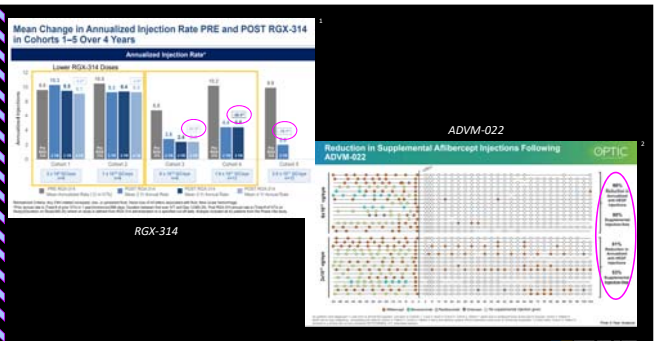
- AAV8-based subretinal therapy that encodes a monoclonal anti-VEGF Fab similar to ranibizumab
- In Phase 1/2a trial, stable-improved visual/anatomic responses
- Suprachoroidal delivery also being studied for wet AMD and DR

ADVM-022

- AAV2.7m8-based intravitreal therapy (ixoberogene soroparvovec) that encodes a molecule similar to aflibercept
- In Phase 1 OPTIC trial, stable-improved visual/anatomic responses
- DME study (INFINITY) halted after SUSAR* reported in spring 2021

*SUSAR – Suspected Unexpected Serious Adverse Reaction

Hot Topic #2: Dry AMD therapeutics



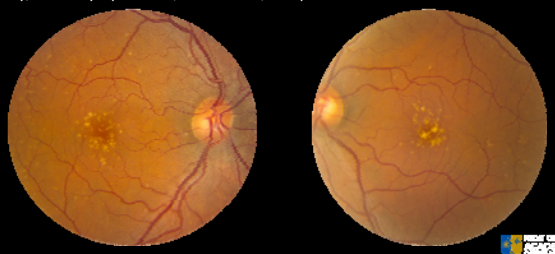
RGX-314

ADVM-022

[1]Campochiaro PA. Presented at 2022 AAO Meeting.
[2]Ragiblo CD. Presented at 2022 Retina Society Annual Meeting.

Patient example

- 67 y/o healthy F politician, non-smoker, first presented in 2017



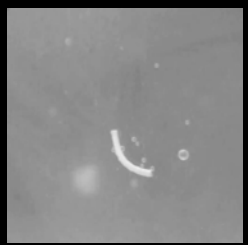
Tyrosine kinase inhibitors (investigational)

OTX-TKI

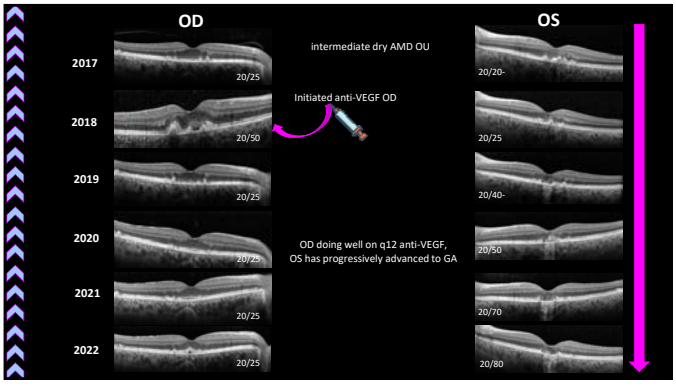
- Axitinib injected intravitreally via biodegradable hydrogel implant
  - In Phase 1b trial, 80% did not require rescue at 6 months with stable mean BCVA and CST

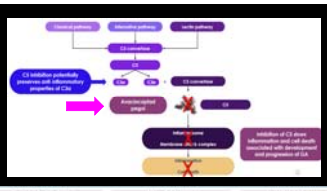
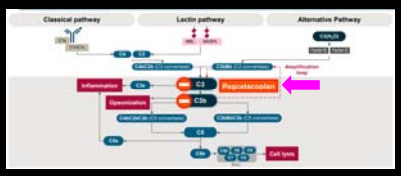
EYP-1901

- Vorolanib injected intravitreally via bioerodible Durasert system
  - In Phase 1 DAVIO trial, 53%/35% pts did not require rescue at 6/12 months with stable mean BCVA and CST



OTX-TKI

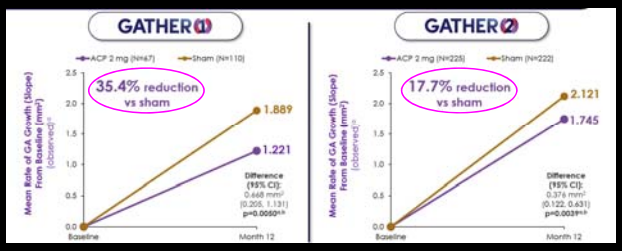


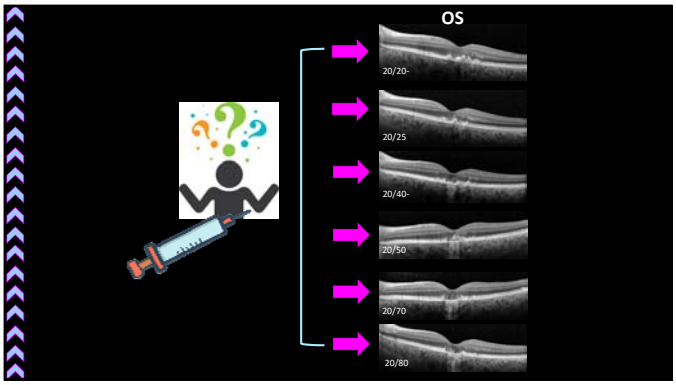
OAKS and DERBY combined

	PM (N=419)	PEOM (N=420)[b]	Sham Pooled (N=417)
New-onset investigator-determined eAMD 12 months, n (%)	25 (6.0%)	17 (4.1%)	10 (2.4%)
New-onset investigator-determined eAMD, 24 months – cumulative, n (%)	51 (12.2%)	28 (6.7%)	13 (3.1%)
Confirmed by reading center, 24 months, n (%) At time of investigator-reported eAMD, 100% of patients had available SD-OCT and 82% had available FA for reading center evaluation	37 (8.8%)	23 (5.5%)	11 (2.6%)

	GATHER2 12 months[1]		GATHER1 12 months[2,a]	
	ACP 2 mg (N=225)	Sham (N=222)	ACP 2 mg (N=67)	Sham (N=110)
Total CNV, n (%)	15 (6.7)	9 (4.1)	6 (9.0)	3 (2.7)



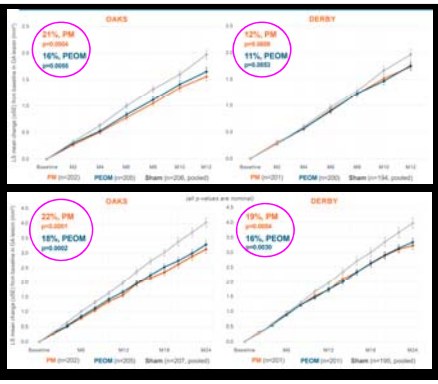
Avacincaptad pegol



12-month results (primary endpoint)

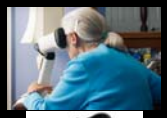
Pegcetacoplan

24-month results



Hot Topic #3: Home monitoring

Home monitoring systems



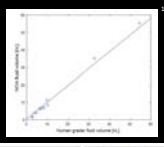
ForeseeHome (FDA-approved)

Notal Home OCT (investigational, Breakthrough Device designation)

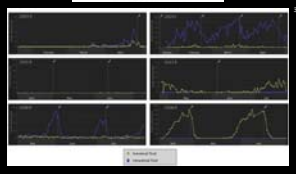
Hot Topic #4: Gene therapy

Home OCT (investigational)

- Excellent usability[1-3]
  - 88-97.6% were able to complete and obtain adequate-quality scans without assistance
  - 41-42s acquisition time
- Accurate detection of fluid[1-3]
  - 83-95% agreement between NOA (AI-based algorithm from Notal Vision) and human grader
    - Most discrepancies involved a very small amount of fluid



[1]



[1]

[1]Keenan TDL, et al. *Ophthalmol Sci*. 2021 Jun 26;1(2):100034.
[2]Kim JE, et al. *BMC Ophthalmol*. 2022 Jun 10;22(1):261.
[3]Liu Y, et al. *Ophthalmol Retina*. 2022 Jul;6(7):575-85.

Gene therapy is a burgeoning space

FDA NEWS RELEASE

FDA Continues Strong Support of Innovation in Development of Gene Therapy Products

Guidances issued today provide regulatory clarity for product developers

For Immediate Release: January 28, 2020

This is a pivotal time in the field of gene therapy as the FDA continues its efforts to support innovators developing new medical products for Americans and others around the world. To date, the FDA has approved four gene therapy products, which insert new genetic material into a patient's cells. The agency anticipates many more approvals in the coming years, as evidenced by the more than 900 investigational new drug (IND) applications for ongoing clinical studies in this area. The FDA believes this will provide patients and providers with increased therapeutic choices.

[1]US Food & Drug Administration. https://www.fda.gov/news-events/press-announcements/fda-continues-strong-support-innovation-development-gene-therapy-products.

Lingering questions about Home OCT

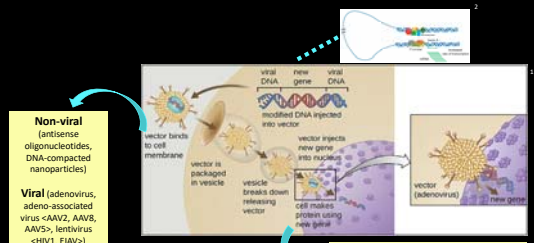
- How we will use it—detection of conversion to wet AMD vs. guiding treatment?
  - May be particularly helpful in those receiving longer-durability treatments
  - DRCR Retina Network developing a clinical trial comparing outcomes in wet AMD patients treated via standard treat-and-extend versus home OCT-guided approach—launch in 2023!
- Integration into workflow
- Reimbursement
- Applications to other diseases

Many types of gene therapy exist

Genetic disease type	Gene therapy type	Examples
Autosomal recessive "Loss-of-function" IRDs*	Gene augmentation (replacement, supplementation)	Voretigene neparvovec-rzyl (*Spark*)
Autosomal dominant "Gain-of-function" IRDs*	Gene suppression/inactivation +/- gene augmentation	siRNA (small interfering RNA), antisense oligonucleotides (ASO)
	Gene editing	CRISPR**-Cas9 technology e.g., AGN-151587/EDIT-101 (*Editas/Allergan*)
Multifactorial	Biofactory	RGX-314 (*REGENXBIO*), ADVM-022 (*Adverum*)

**inherited retinal diseases*
***clustered regularly interspaced short palindromic repeats*

Gene therapy mechanism of action



Non-viral (antisense oligonucleotides, DNA-compacted nanoparticles)

Viral (adenovirus, adeno-associated virus <AAV2, AAV8, AAV5>, lentivirus <HIV1, EIAV>)

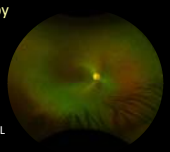
Native protein (RPE65)

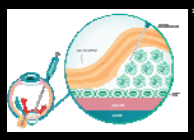
Non-native protein (anti-VEGF fab)

[1]Image courtesy of Rice University under A CC by 4.0 License. https://www.ophthalmologymanagement.com/issues/2019/july-2019/introduction-to-gene-therapy.
[2]Xia J, Wei G. *Cells.* 2019;8(10):1281.

Voretigene neparvovec-rzyl (Luxturna™)

- First FDA-approved gene therapy (December 2017)
  - Administered at 10 US treatment centers
- Adeno-associated virus vector (AAV2)-based subretinal gene therapy
  - 1.5 x 10^{11} vector genomes (vg)/0.3 mL
- Indicated for patients with:
  - Confirmed biallelic *RPE65* mutation-associated retinal dystrophy (Leber congenital amaurosis type 2, certain variants of retinitis pigmentosa) &
  - Viable retinal cells
- $425,000 drug cost per eye



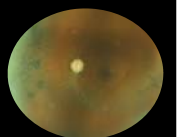


[1]http://www.luxturnahcp.com/how-LUXTURNA-works/mechanism-of-action/#isi.
[2]http://www.mysparkgeneration.com/hcp-support.html#TreatmentCenters.

Ocular gene therapy targets many diseases

- Achromatopsia
- Choroideremia
- Diabetic macular edema
- Diabetic retinopathy
- Leber congenital amaurosis 2
- Leber congenital amaurosis 10
- Leber's hereditary optic neuropathy
- Neovascular AMD
- Non-neovascular AMD
- Retinitis pigmentosa
- Stargardt disease
- Usher syndrome 2A
- X-linked retinoschisis

Choroideremia



Retinitis pigmentosa

Leber congenital amaurosis 2

[1]Venckus T. Choroideremia. https://webeye.ophth.uiowa.edu/eyeforum/atlas/pages/Choroideremia.htm.

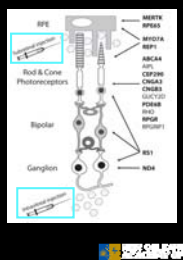
Outcomes of voretigene neparvovec-rzyl

- Visual function data is critical in holistically assessing outcomes of VN patients
  - Phase 3 trial primary outcome was change in performance on multi-luminance mobility test (MLMT) at 1 year[1]
  - In the PASS interim analysis, there was no significant change (>0.3 logMAR) in VA post-VN, but mean FST decreased from baseline, representing improved light detection[2]
- In a multicenter case series of 77 eyes in 41 patients (16 adults/25 children), baseline VA, intraoperative foveal detachment, or patient age did not have a significant effect on mean VA change at 1 year[3]
  - 16/17 eyes that improved ≥2 lines were of pediatric patients
- Consensus recommendations for gene therapy eligibility being developed[4]

[1]Russell S, et al. *Lancet.* 2017;390(10097):849-60.
[2]Nagiel A, et al. Paper presentation at the 2021 Retina Society Annual Meeting, Chicago, IL. October 1, 2021.
[3]Sengillo JD, et al. *Ophthalmol Retina.* 2022 Apr;6(4):273-83.
[4]Sodi A, et al; Italian IRD Working Group. *Orphanet J Rare Dis.* 2021 Jun 4;16(1):257.

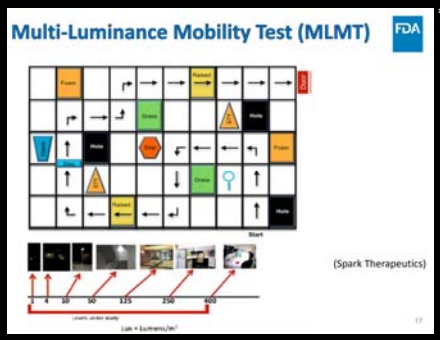
Ocular gene therapy targets many diseases

- Injection approach generally guided by location of targeted cells, but no consensus on optimal approach

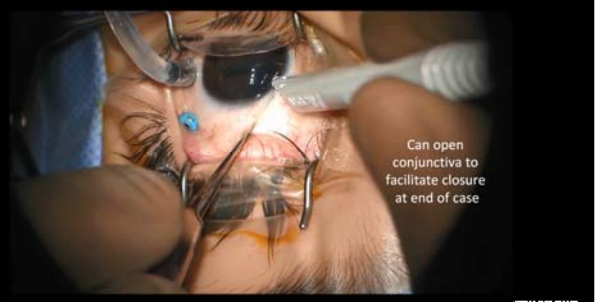


[1]Trapani I, et al. *Human Molecular Genetics.* 2019;28(1):108-18.
[2]Lee KJ. https://www.aao.org/headline/suprachoroidal-injection-of-triamcinolone-meets-pr.
[3]Orbit subretinal delivery system. http://www.orbitsds.com.

Multi-Luminance Mobility Test (MLMT)

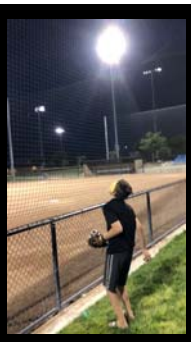


[1]https://www.fda.gov/media/108598/download.



CYW: 25g PPV/subretinal voretigene/AFX OS

Untreated eye (OS)



Treated eye (OD)

Courtesy of J. Timothy Stout, MD, PhD, MBA; used with permission of patient and parents.

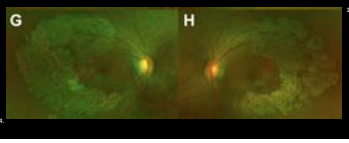
CYW: 25g PPV/subretinal voretigene/AFX/iOCT OD

thank you / questions

contact: <christina.weng@bcm.edu>

Questions that remain re: gene therapy

- Optimal delivery approach?
- How to identify a good surgical candidate? Ideal age to treat in IRDs?
- Best surgical technique (e.g., hyaloid elevation? location/volume of bleb?)
- Are associated pigmentary changes clinically meaningful?
- Consequences of constitutively active transgene end-product?
- Long-term durability of tx? Is re-treatment possible?
- Accessibility as more gene tx becomes available?



[1]Ganga WS, et al. *Ophthalmol Retina*. 2022 Jan;6(1):58-64.