ProQR®

ProQR R&D DAY

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JANUARY 29, 2019, NEW YORK

Forward looking statements

This presentation contains forward-looking statements. All statements other than statements of historical fact are forward-looking statements, which are often indicated by terms such as "anticipate," "believe," "could," "estimate," "expect," "goal," "intend," "look forward to", "may," "plan," "potential," "predict," "project," "should," "will," "would" and similar expressions. Such statements include those relating to our ProQR Vision 2023 strategy and our key 2019 goals, the development and therapeutic potential of our product candidates, including sepofarsen, QR-1123, QR-421a, QR-411a, QR-504, the potential of our Axiomer® editing platform, our plans and timing of initiating and obtaining results from our ongoing and planned clinical trials, our plans for building commercial infrastructure to support the launch of our product candidates, if approved, our plans and timing of submitting applications for and receiving marketing approval of our product candidates, our expectations for our platform and discovery of new product candidates, and our plans for strategic collaborations and alliances for our programs..

Forward-looking statements are based on management's beliefs and assumptions and on information available to management only as of the date of this press release. Our actual results could differ materially from those anticipated in these forward-looking statements for many reasons, including, without limitation, the risks, uncertainties and other factors in our filings made with the Securities and Exchange Commission, including certain sections of our annual report filed on Form 20-F. These risks include, but are not limited to, any one or more of our product candidates will not be successfully developed or commercialized, the risk of cessation or delay of any ongoing or planned clinical trials, we may not realize the intended benefits of our current and potential future strategic collaborations, we may not discover or develop any new product candidates, including through our Axiomer® platform, that prior results observed from preclinical or clinical trials, will not be replicated or will not continue in ongoing or future studies or trials, that we may not successfully submit applications for marketing approval for our product candidates on time or at all, that regulatory authorities may require additional clinical trials beyond those that we currently contemplate conducting, that we will be unable to obtain and maintain regulatory approval for our product candidates, the risk that the size and growth potential of the market for our product candidates will not materialize as expected, risks associated with our dependence on third-party suppliers and manufacturers, risks regarding the accuracy of our estimates of expenses and future revenue, risks relating to our capital requirements and needs for additional financing, and risks relating to our ability to obtain and maintain intellectual property protection for our product candidates. Given these risks, uncertainties and other factors, you should not place undue reliance on these forward-looking statements, and we assume no obligation to update these forward-looking statements, even if new information becomes available in the future, except as required by law.

Agenda

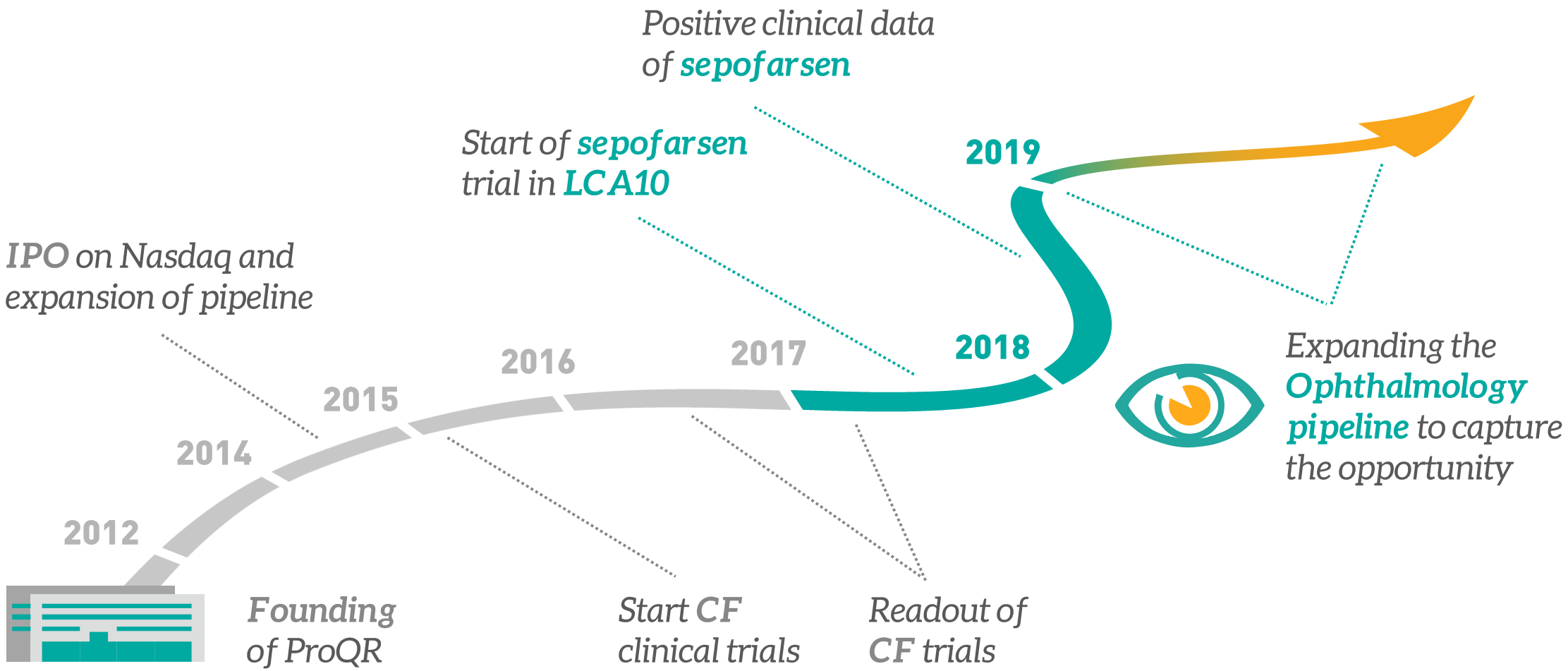
8:00 – 8:05	**Smital Shah** *Chief Business and Financial Officer*	
8:05 – 8:20	**Daniel de Boer** *Founder & Chief Executive Officer*	
8:20 – 8:35	**Aniz Girach, MD** *Chief Medical Officer*	
8:35 – 9:20	**David Rodman, MD** *Executive Vice President of Research & Development*	
9:20 – 9:30	Q&A	
9:30 – 10:00	Break	

10:00 – 10:20	**Thaddeus (Ted) Dryja, MD** *Professor of Ophthalmology*	
10:20 – 10:45	**Peter Adamson, Ph.D.** *Head of Ophthalmology Research*	
10:45 – 11:00	**Gerard Platenburg** *Chief Innovation Officer*	
11:00 – 11:10	Q&A	
11:10 – noon	Lunch	

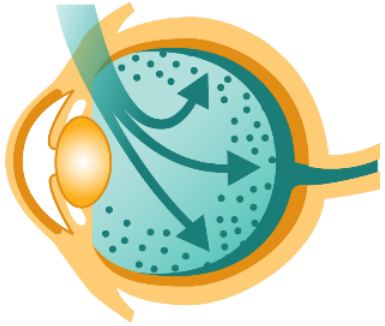
ProQR's Vision 2023

Daniel A. de Boer, *Founder & Chief Executive Officer*

The ProQR Journey

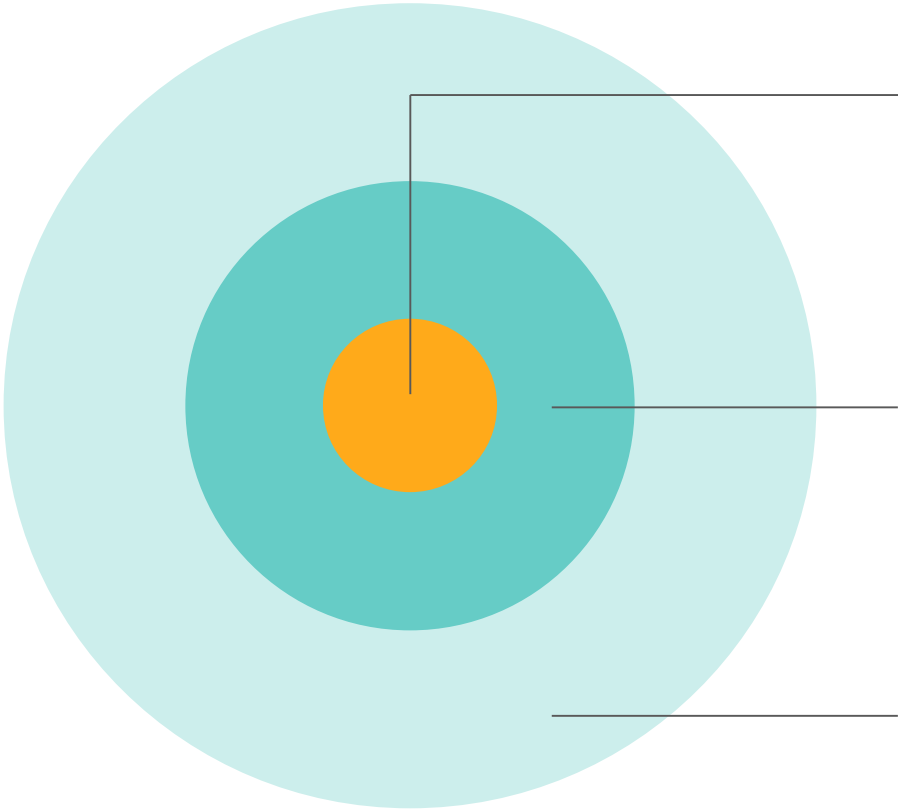


Eyes on the Opportunity



Foundation of common characteristics, irrespective of the target

- Intravitreal administration is routine procedure
- Acceptable safety profile
- Broad distribution throughout the entire retina
- Long half life allowing for infrequent dosing



The opportunity:

>100 tangible targets remain after further filtering for disease state and population size

ProQR projects its technology can address about **25% of the mutations** at a molecular level

>300 genes causing Inherited Retinal Diseases, described with **>50 pathogenic mutations** per gene, leading to **>15,000 targets**.

ProQR's VISION2023

A FULLY INTEGRATED INHERITED RETINAL DISEASE COMPANY BY 2023

2 COMMERCIAL PRODUCTS

3 LATE STAGE PROGRAMS

7 EARLY STAGE PROGRAMS

ProQR's VISION2023

THE 3 PILLARS OF VISION 2023

Discovery engine

- Specialized integrated discovery engine
- Discovering 10 or more new IRD drugs per year
- Use human optic cups to pre-clinically validate clinical molecules

Development

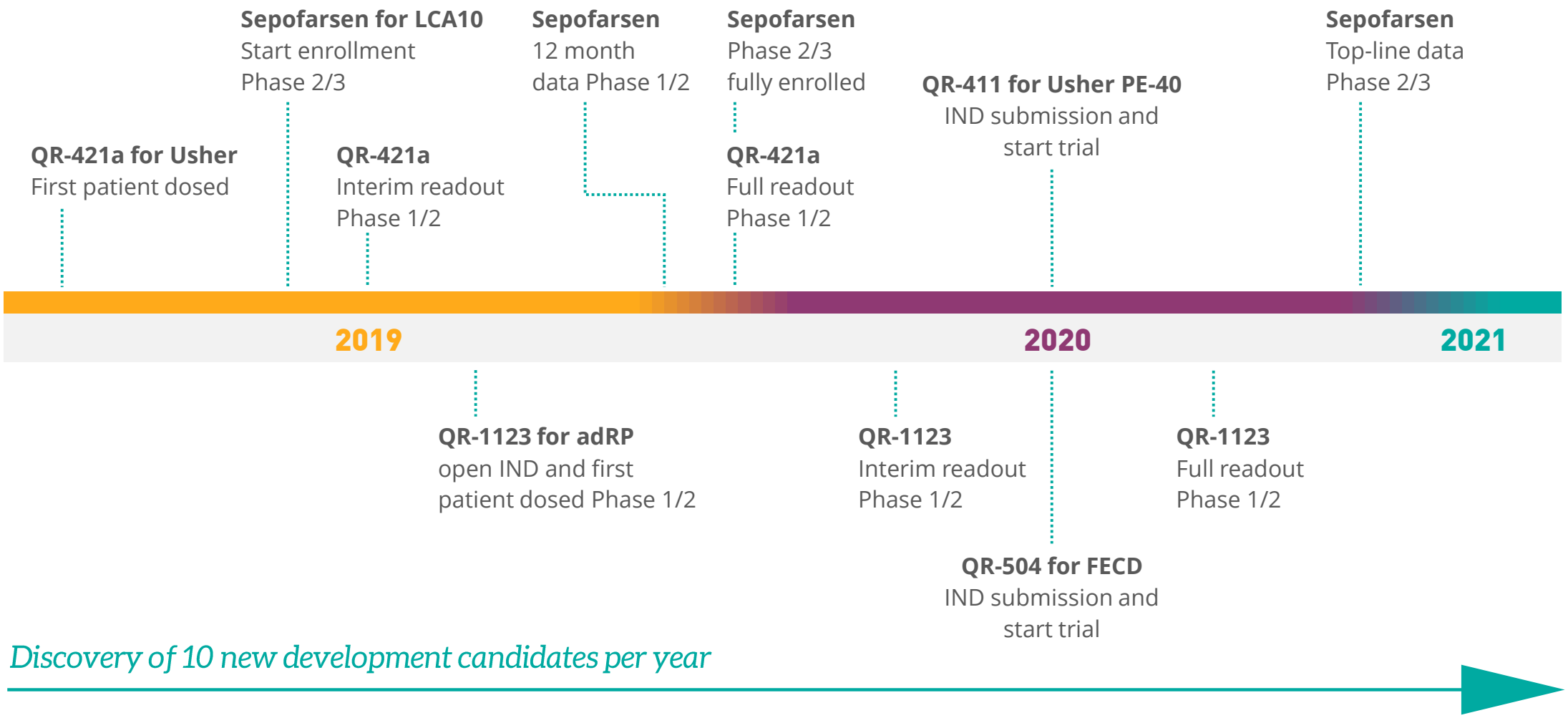
- Utilize digital clinical trials
- Use innovative Bayesian adaptive designs to accelerate time to NDA / MAA

Commercial

- Establish IRD specialized commercial infrastructure in North America and Europe
- Focused on ~approx. 30 specialist centers that treat majority of IRD patients
- Leverage commercial infrastructure for multiple products to same call points

ProQR key development pipeline

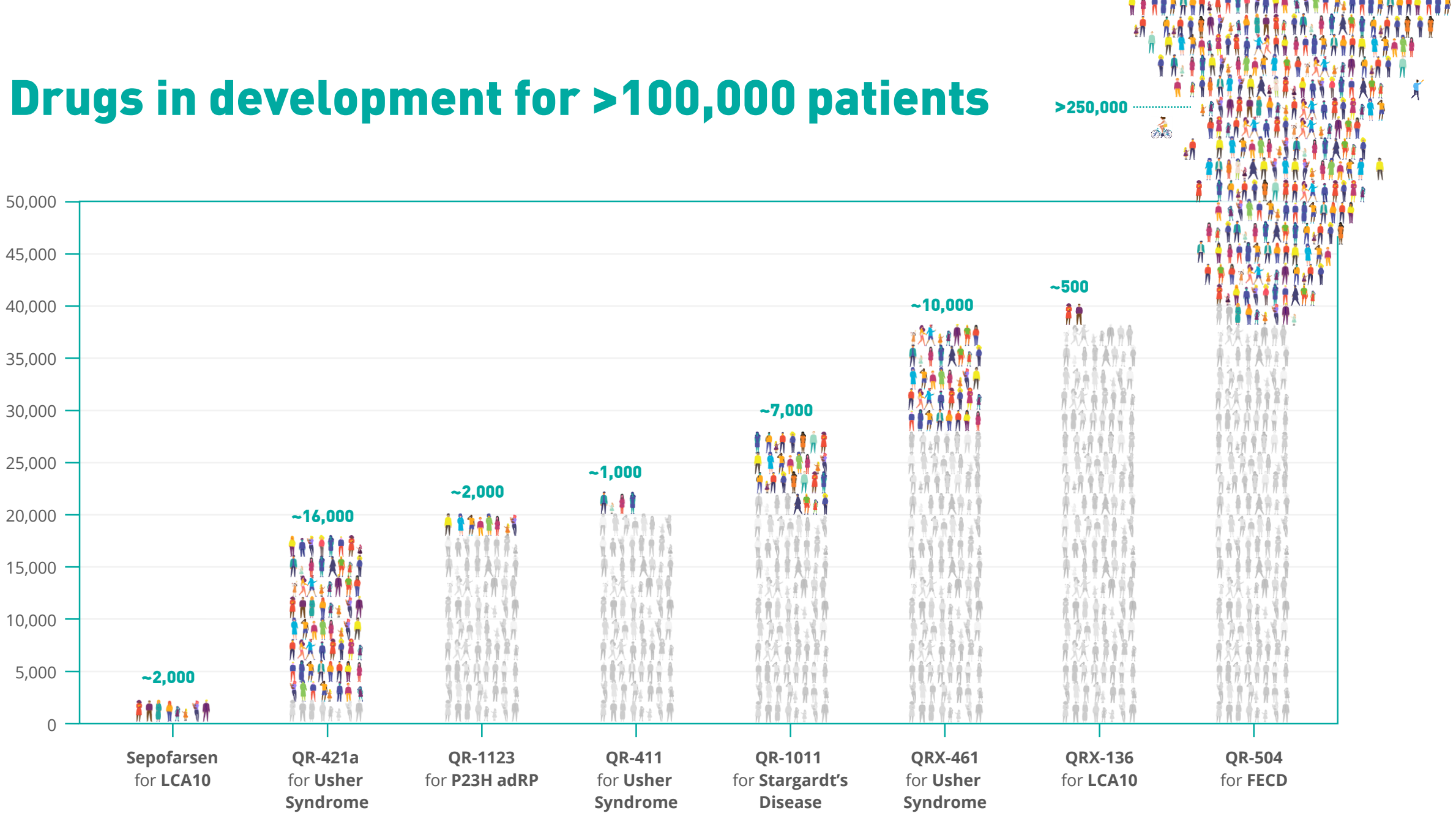
5 IRD drugs in clinical trials in next 18 months



Building ProQR's commercial infrastructure

- Patients are typically seen at one of the approximately 30 IRD hub centers in North America and Europe
- A compact market that can be covered by a limited number of sales reps
- ProQR intends to market multiple IRD products in EU and North America independently, and find partners for ROW
- Pre-commercialization activities underway
  - Building KOL engagement
  - Engaging payers and exploring innovative reimbursement models
  - Launch planning for sepofarsen launch in 2021

Drugs in development for >100,000 patients



ProQR's VISION2023

A FULLY INTEGRATED INHERITED RETINAL DISEASE COMPANY BY 2023

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Aniz Girach, MD – Chief Medical Officer

- Most recently **Chief Medical Officer at Nightstar Therapeutics** overseeing development of **gene therapies** for IRD
- Experience in academia and industry at **Eli Lilly, Merck, Alcon** and ThromboGenics
- Oversaw **development and approval** of Ocriplasmin (Jetrea) a first in class **biologic therapy** for retinal disease
- **Honorary Professorship** at Wills Eye Hospital, Philadelphia
- Member of **3 Scientific Advisory Boards** for international ophthalmic organizations currently
- **Reviewer for 5 peer-reviewed journals**, including Eye and IOVS
- Edited 4 books and author of **over 100 scientific abstracts and manuscripts**

RNA therapies for IRDs

Aniz Girach, MD, *Chief Medical Officer*

Opportunity of RNA therapies for IRDs

- **High unmet medical need**
- Rational design/ broad applicability
- Ease of delivery, wide distribution
- Acceptable safety profile
- Promising efficacy

IRD management coming of age

- **Improved diagnosis**
- **New Treatment options**
  - Gene therapies
    - Luxturna for LCA2
    - Experimental therapies for other IRDs
      - Eg choroideremia, RP
  - RNA therapies
    - Macugen for Wet AMD
    - Vitravene for CMV Retinitis
    - Experimental therapies for other IRDs
      - Eg ASO for LCA10, Usher syndrome

How do RNA oligonucleotide drugs compare with gene therapy?

RNA Oligonucleotide Therapy	Gene Therapy/Editing
Specific	Specific (replaces or edits)
Requires re-dosing	Potential one and done dosing
Naked, no vectors needed	Editing material is contained within viral vectors
Under local anesthesia	Usually requires general anesthesia
Reversible	Irreversible
Intravitreal Injection	Sub-retinal surgery with vitrectomy
Can be used in earlier disease, since central/peripheral retinal exposure	Usually suitable for end-stage disease only, since applied to sub-macular area

Opportunity of RNA therapies for IRDs

- High unmet medical need
  - **Rational design/ broad applicability**
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Rational design: efficient lead selection in ophthalmology

Efficient *in silico* screen

25 AONs screened on average

Lead molecule selected

Selection based on

- Splice-factor prediction
- Off-target binding
- Target RNA –oligo binding
- Thermodynamic properties

Selection based on

- *In vitro* efficacy (including retinal organoid model)
- Low immunogenicity
- Low toxicity
- Good manufacturability

Opportunity of RNA therapies for IRDs

- High unmet medical need
- Rational design/ broad applicability
  - **Ease of delivery, wide distribution**
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RNA therapy delivery and distribution

EASE OF DELIVERY AND BROAD RETINAL DISTRIBUTION

Intravitreal delivery is routine procedure

- Routine procedure allows wide patient accessibility
- Long half-life in the eye allows for dosing 2-4 times per year or less frequent
- Chemical modifications enable naked delivery

Broad distribution allows for targeting of central and peripheral diseases

- Oligo's distribute broadly to all different cell types and layers, including retina and cornea
- Suitable for targeting central and peripheral disease

Comparing intravitreal delivery of RNA to subretinal delivery used in gene therapy

RNA Therapy

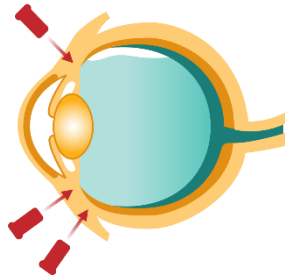
Intravitreal administration

Injection in side of the eye depositing the drug in the vitreous for broad delivery throughout all cell layers in the eye

Gene Therapy

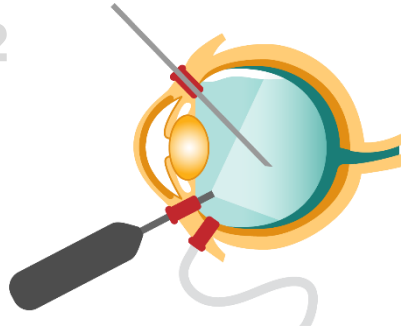
Sub-retinal surgery used for delivery

1



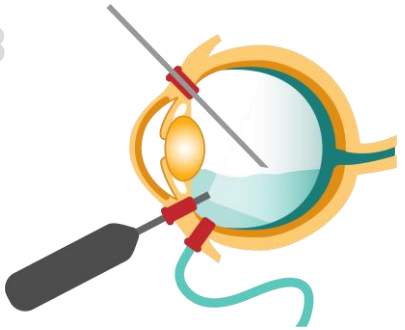
3 ports are generated in the wall of the eye to allow access for tools

2



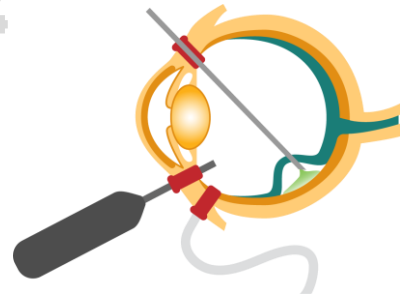
A light and a needle are inserted into the eye to locate the place of injection

3



Vitrectomy: The vitreous gel is cut/sucked out of the eye to aid visualization and ease of injection

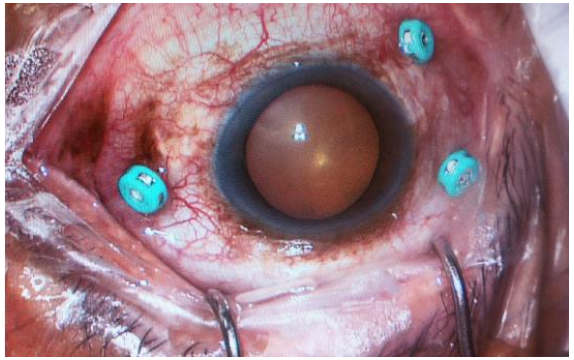
4

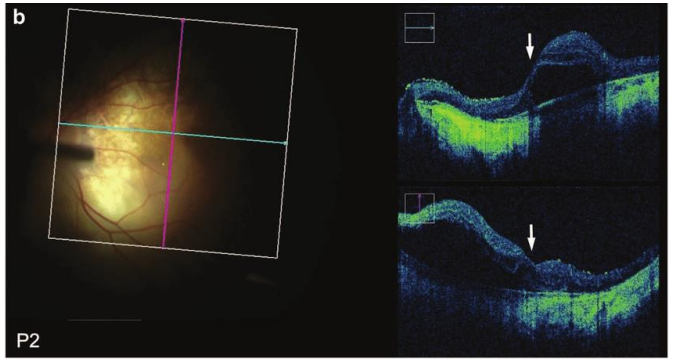


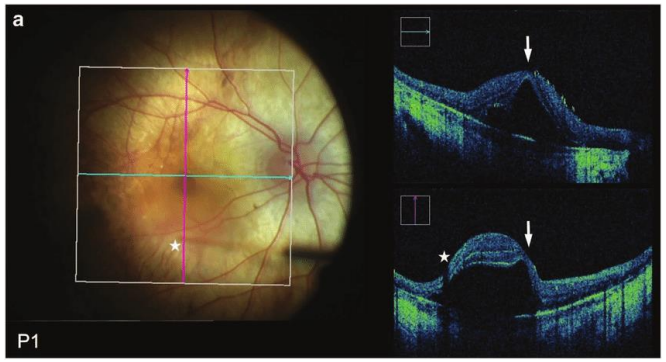
The needle enters the retina, lifting off the retina until a bleb is formed, then depositing drug in the subretinal space

Complications of subretinal surgery

- Sub conjunctival hemorrhage/ chemosis
- Enlargement of sclerotomies with thin sclera/prior surgery
- Losing tunnels in trocar insertion
- Suprachoroidal hemorrhage/subretinal infusion
- Accidental removal of infusion
- Vitreoretinal incarceration at sclerotomies
- Leaking entry sites
- Endophthalmitis
- Cataract development
- Lens subluxation
- Anterior chamber flattening
- Posterior capsule rupture/zonular dialysis
- PVD induction complications
- Intraoperative complications with tamponades
- Iatrogenic retinal tears
- Retinal detachment
- Raised IOP
- Intraoperative hemorrhages
- Macular folds
- Loss of vision
- Hypotony related complications
- General anesthesia complications







Gupta OP et al. Ophthalmic Surg Lasers Imaging 2007;38:270-5.

Complications due to IVT/drugs

Complications of IVT injection

- Infection
- Hemorrhage
- Wound leakage
- Lens touch/cataract
- Increased IOP

Complications due to IVT drugs

- Inflammation/immunogenicity
- Retinal/macular edema
- Arterial thrombo-embolic events*
- Retinal degeneration
- Cataracts
- Retinal detachment

* Lucentis: Most commonly used IVT drug, has arterial thrombo-embolic event rate 10.4-10.8%; Stroke rate 2-4.8% (Source: Lucentis PI)

AEs are manageable with most IVT drugs

Opportunity of RNA therapies for IRDs

- High unmet medical need
- Rational design/ broad applicability
- Ease of delivery, wide distribution
  - **Acceptable safety profile**
- Promising efficacy

Sepofarsen: manageable safety profile

	Drug	Indication	Lens Opacities	Lens Replacement	CME/Retinal Edema	Increased IOP	Inflammation
IVT	Iluvien	DME	82%	80%	ND	34%	2%
IVT	Ozurdex	DME	68%	61%	ND	28%	2%
IVT	Yutiq	Uveitis	56%	ND	11%	22%	3%
IVT	Macugen	wAMD	10-40%	ND	1-5%	10-40%	1-5%
IVT	Lucentis	wAMD/DME	11-28%	ND	5-11%	7-24%	1-18%
IVT	Vitravene	CMV Retinitis	5-20%	ND	5-20%	ND	7-10%
IVT	**Sepofarsen* 80µg dose**	**LCA10**	**50%**	**16%**	**Not observed****	**Not observed**	**Not observed**
Subretinal	Luxturna	LCA2	20%	ND	ND	15%	5%
Subretinal	Post Vitrectomy***	IRD Gene therapy	45%	37%	ND	ND	ND

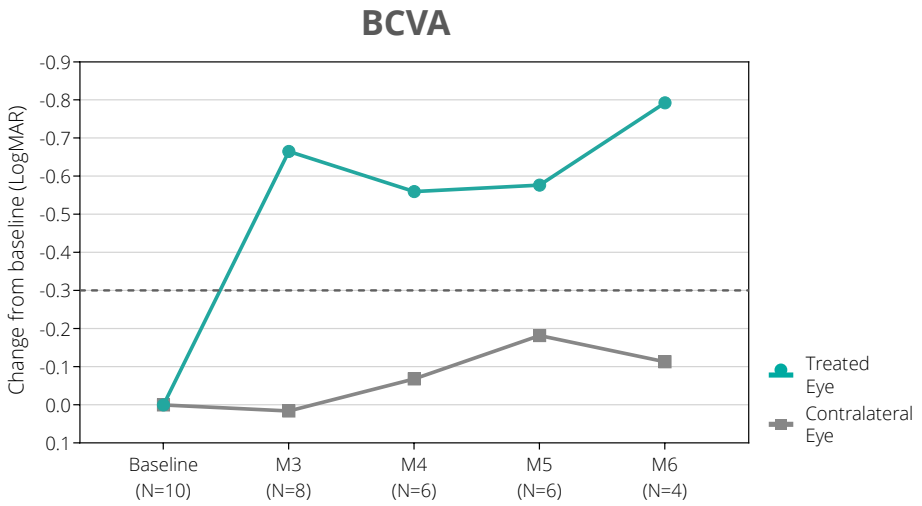
*Ph 1/2 80µg dose group (pivotal dose) ** CME was seen in 160µg dose group in the Ph 1/2 trial ***Feng et al, 2014 ND: non-disclosed in Prescribing Information

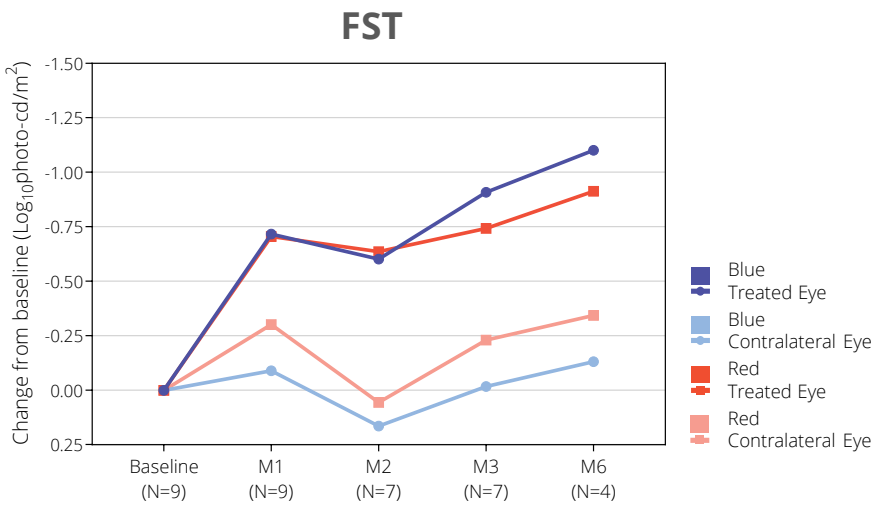
Lens opacities and CME are manageable in routine clinical practice

Opportunity of RNA therapies for IRDs

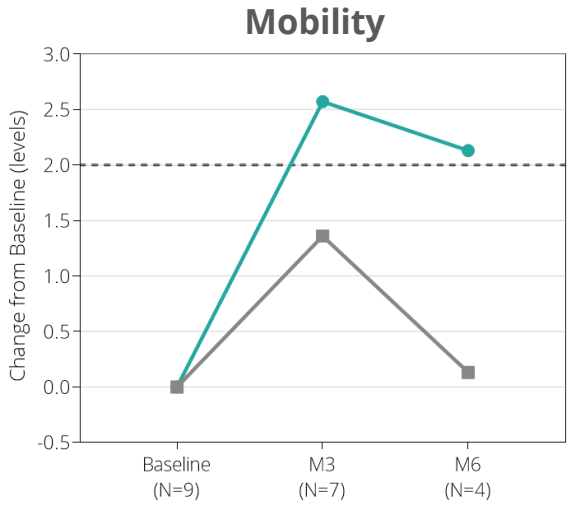
- High unmet medical need
- Rational design/ broad applicability
- Ease of delivery, wide distribution
- Acceptable safety profile
  - **Promising efficacy**

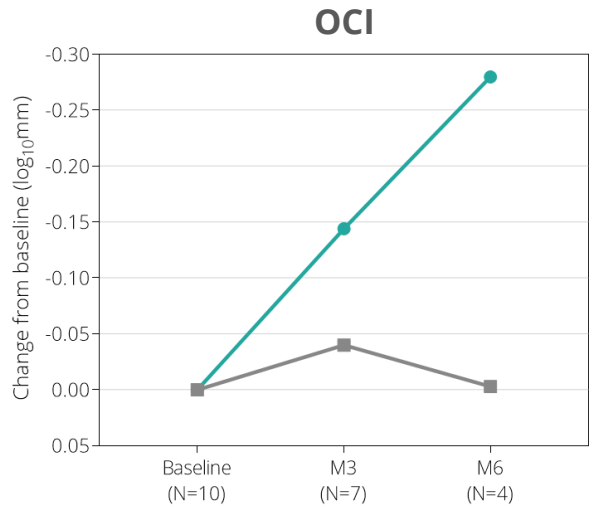
Promising efficacy observed for sepofarsen





First time in severe photoreceptor disease, a meaningful concordant response seen across all end points





Opportunity of RNA therapies for IRDs

- High unmet medical need
- Rational design/ broad applicability
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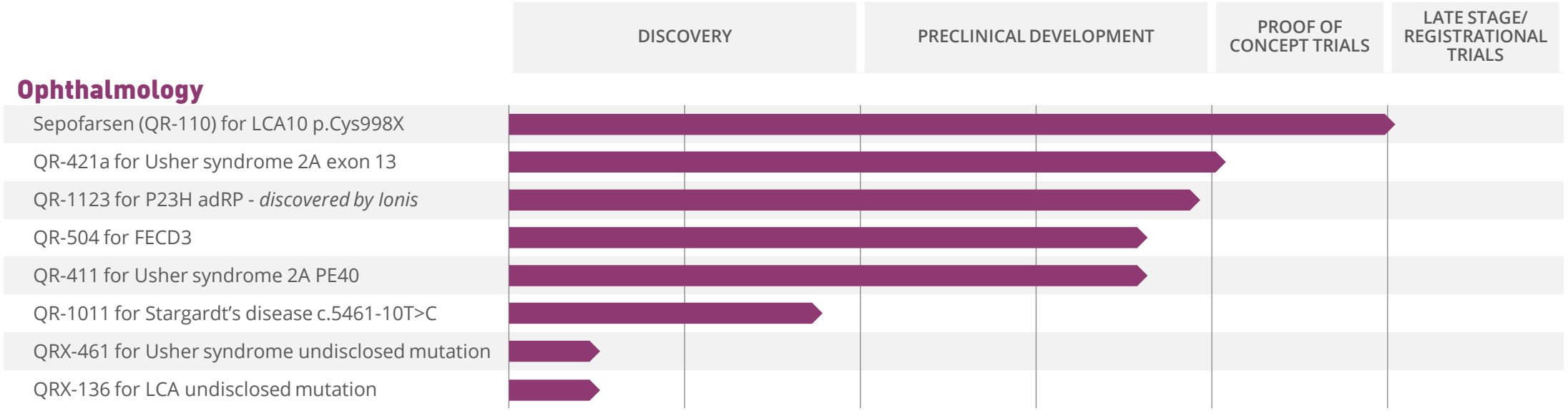
Inherited Retinal Dystrophies

A major opportunity for ProQR RNA therapeutics

David Rodman, MD, *Executive Vice President of Research & Development*

Ophthalmology pipeline

Building on success of sepofarsen

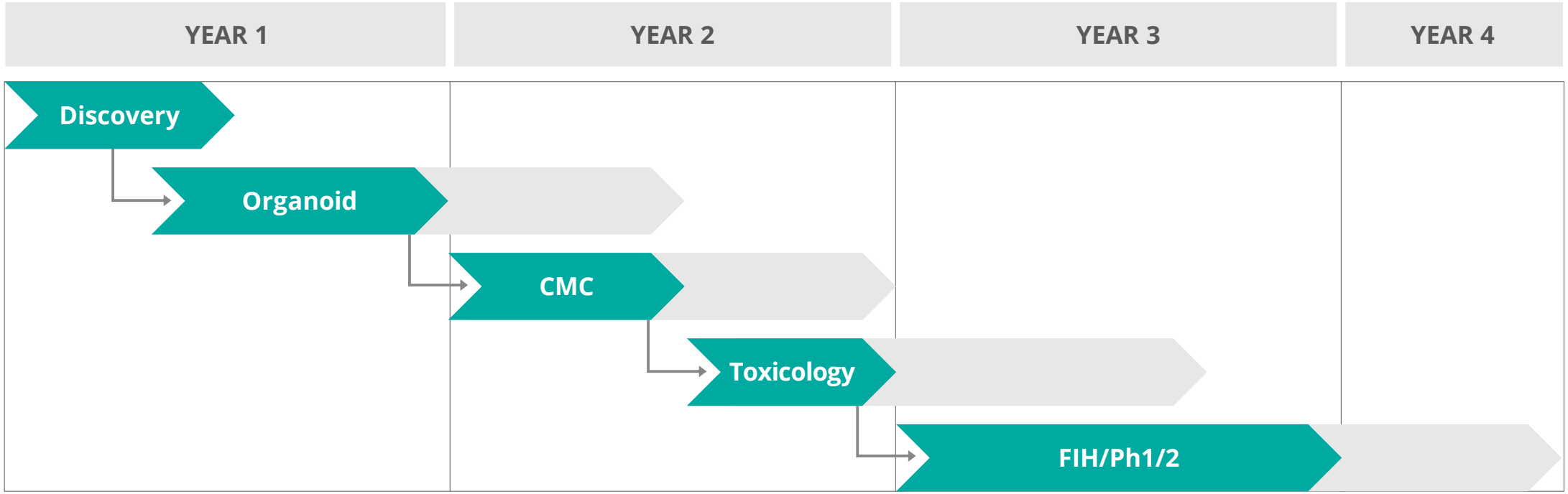


- Acceptable risk/benefit safety profile (sepofarsen)
- Durable response with infrequent dosing
- Intravitreal administration delivers to the retina
- Clinically meaningful vision improvement in a majority of low vision patients

- Optic cup accurately predicted:
  - Clinically efficacious intravitreal dose level
  - Response to treatment
  - Time to onset of response
- To be further validated in future trials of sepofarsen and other IRD programs

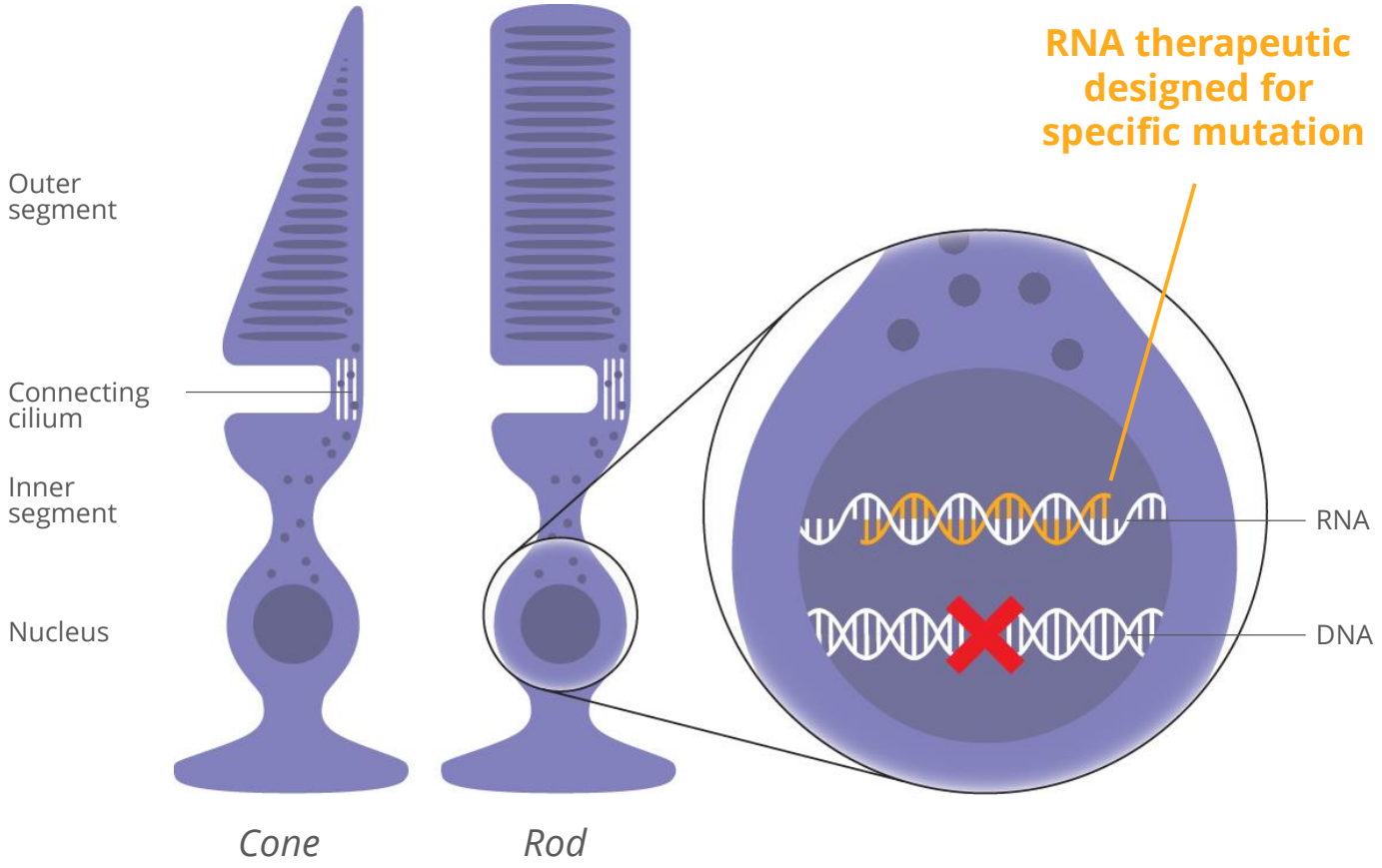
Efficient, predictive translational platform

Three years from target selection to start of pivotal program



ProQR Ophthalmology leverages

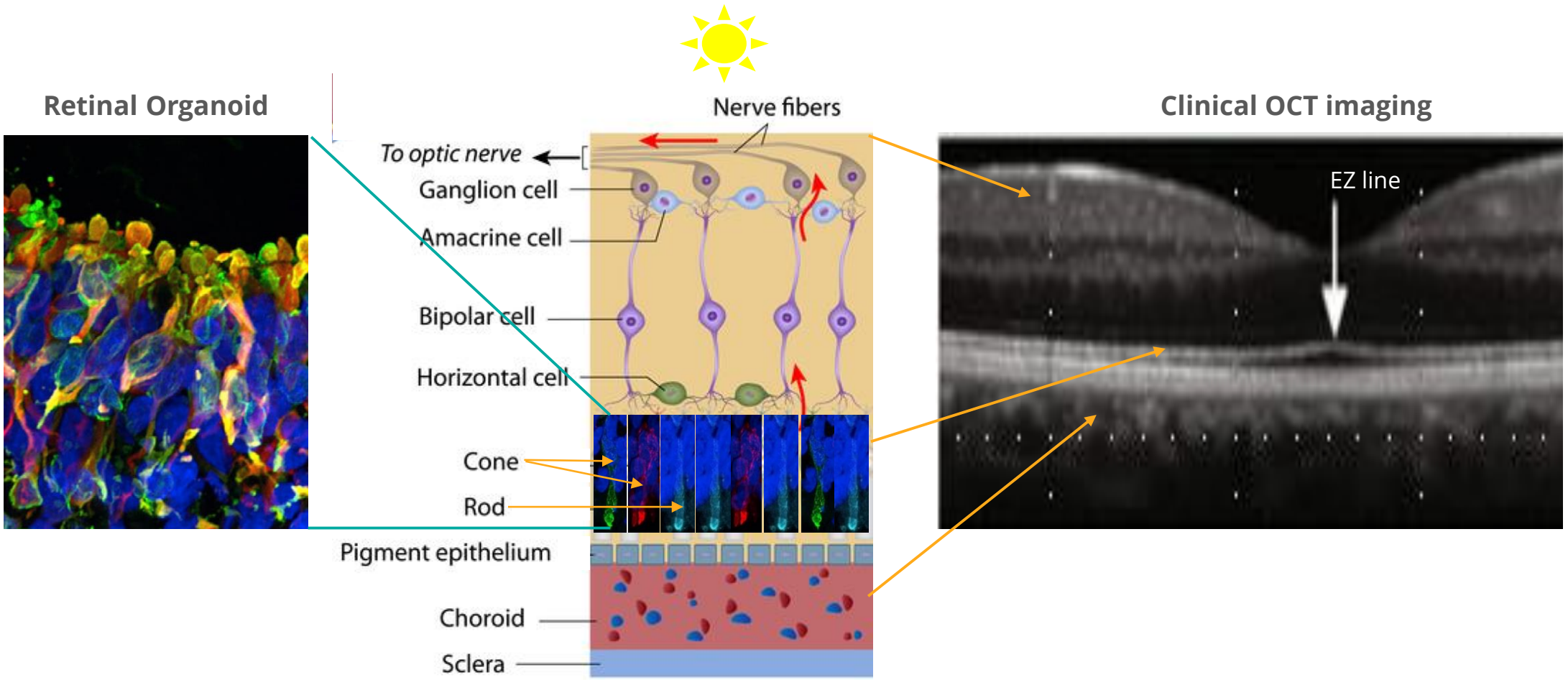
Platform synergies with potential to treat ~300 diseases



- Efficient rational drug design
- Predictive human-derived ex vivo organoid screening platform
- Long tissue half-life supports an optimized dosing regimen
- Rapid clinical development leading to broad platform de-risking

Translation from retinal organoids to clinical trials

Restoration of cilium and outer segment in LCA10 and Ush2a



Efficient, predictive translational platform

Three years from target selection to start of pivotal program

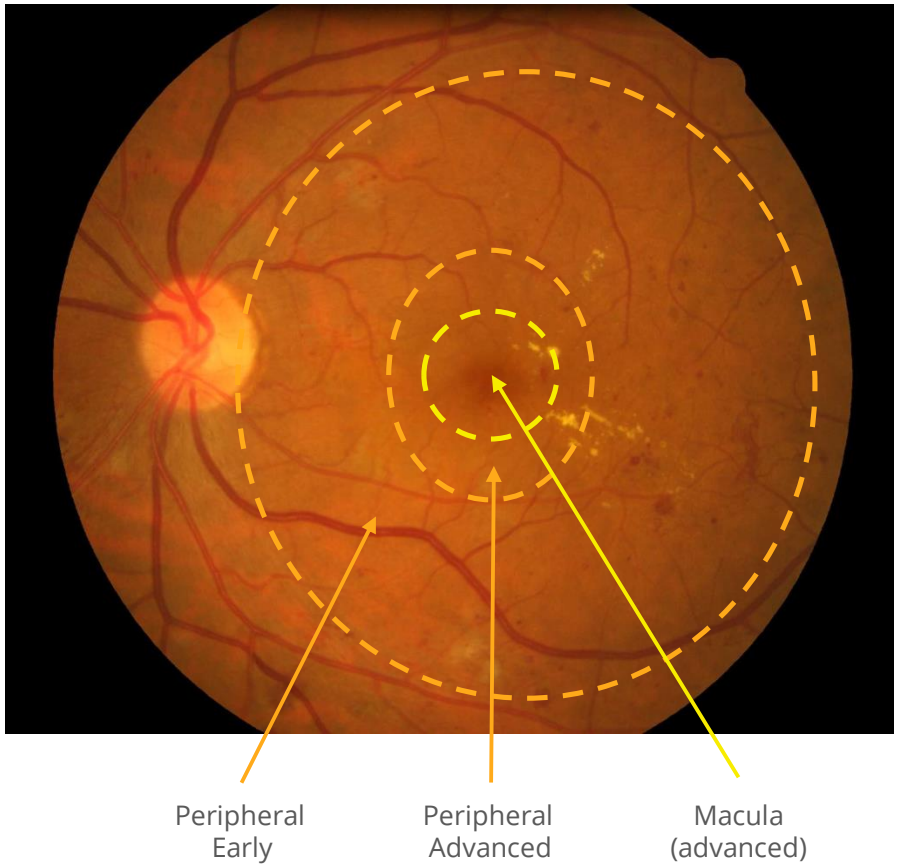
Stage 1	Stage 2	Stage 3	Stage 4
1º screen in transfected cells	2º screen in retinal organoid model	GLP NHP PK(/PD) and toxicology	FIH/Phase 1/2 12 month clinical trial
Optimize on-target molecular activity	Characterize naked oligo molecular activity	Generate predictive PK/PD and TK models	Execute proof-of concept (3-6m IA) and dose selection
Trigger organoid model	Trigger CMC	Trigger IND/CTA	Trigger pivotal program
3-6 months	9-12 months	6-12 months	12-18 months

FIH, Phase 1/2 design philosophy

Strong GO triggers accelerated development

	Strong GO	GO	Equivocal	NO GO
Mechanistic PoC – pharmacodynamic endpoint	√	√	-	
Clinical PoC - registration endpoint	√	-	-	
Development dose regimen	+/-	+/-	-	
Safety	√	√	√	x
Preliminary risk/benefit	√	+/-	-	

Initial ProQR disease indications provide broad platform de-risking



Location	1º Outcome measure	ProQR Pipeline	Development Stage
Macula	Visual acuity	Sepofarsen LCA10	Late clinical
		QRX-1011 Stargardt's	Preclinical
Peripheral (moderate to advanced)	Visual fields, Visual acuity	QR-421a Ush2a	Early clinical
Peripheral (early to moderate)	Visual fields	QR-1123 adRP	IND submission
		QR-411 Ush2a	IND-enabling

Snapshot of clinical-stage ophthalmology programs

Progressive platform validation and indication expansion

Compound	Indication	Development Stage	Development De-risking	Status	Next milestone
sepofarsen	LCA10	Pivotal	✓ Photoreceptor delivery ✓ Splice correction ✓ Central retinal efficacy	✓ 3-month efficacy and up to 12 m safety	Start pivotal H1 2019 Ph1/2 trial completion H2 2019
QR-421a	Ush2a	FIH/PoC	• Exon skipping • Peripheral retinal efficacy	Site initiation and screening	Start Phase 1/2 mid-2019
QR-1123	adRP	IND-ready	• RNA knockdown • Allele-specific suppression	IND preparation	Ph 1/2 start H2 2019

Sepofarsen (QR-110) for LCA10

LCA10

Lose sight in first years of life

No therapy available

p.Cys998X mutation affects ~2,000 patients in the Western world

Sepofarsen

Goal: Restore vision/ prevent vision loss in patients with LCA10

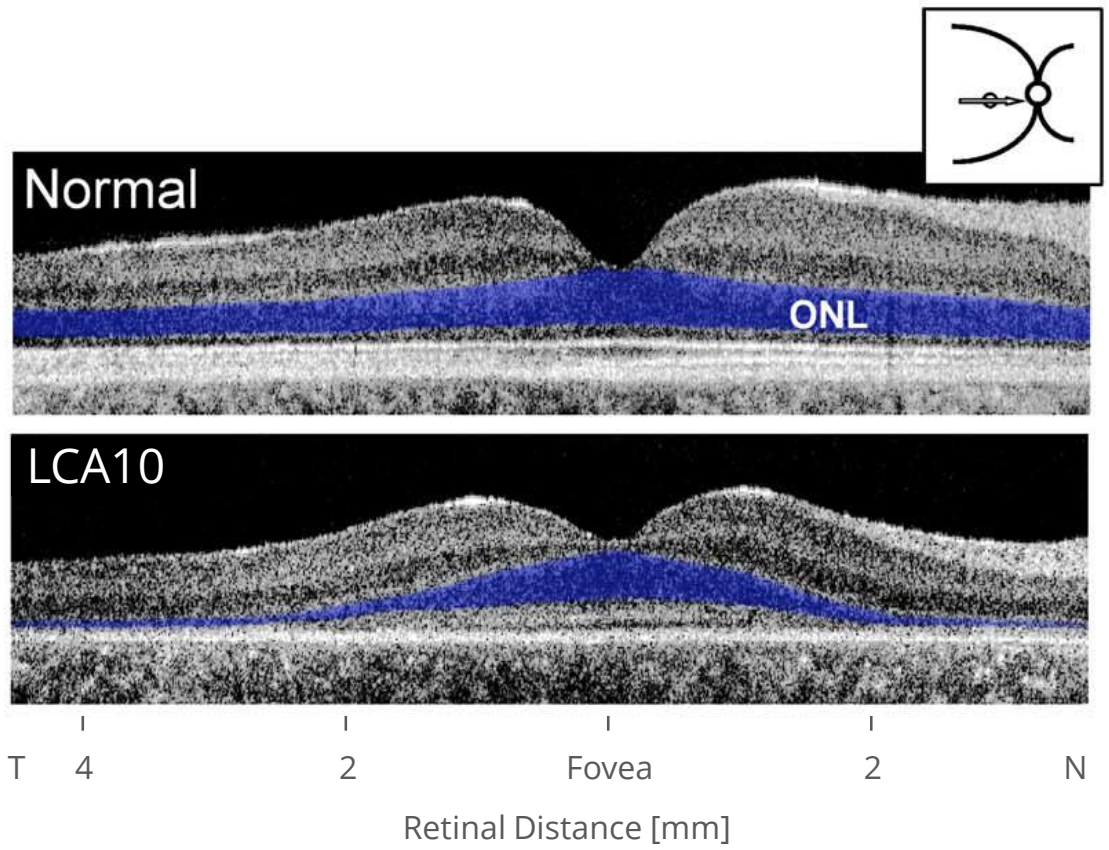
Locally administered in the eye. Routine intravitreal procedure

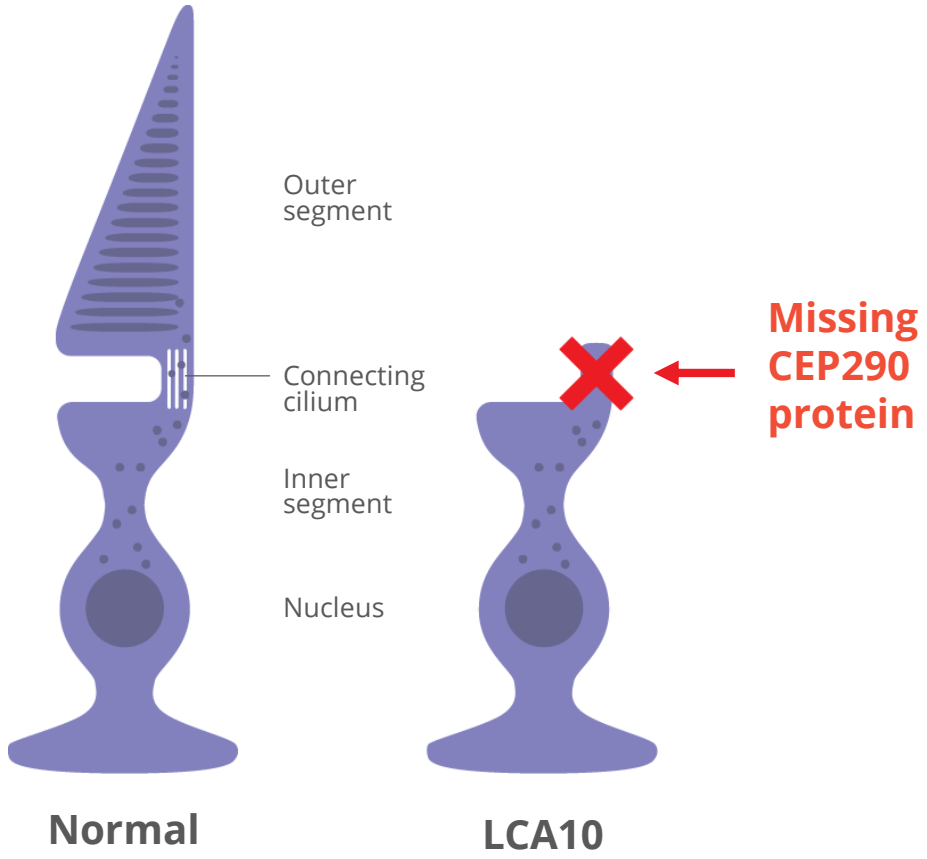
Anticipated infrequent dosing of 2 times a year

- ✓ Established modality in eye
- ✓ Strong preclinical proof of concept in human retina in preclinical models
- ✓ Orphan drug designation
- ✓ Fast track designation
- ✓ Phase 1/2 interim analysis showed rapid and sustained efficacy and favorable safety
- Pivotal phase 2/3 trial expected to start in H1 2019

LCA10 Clinical Phenotype

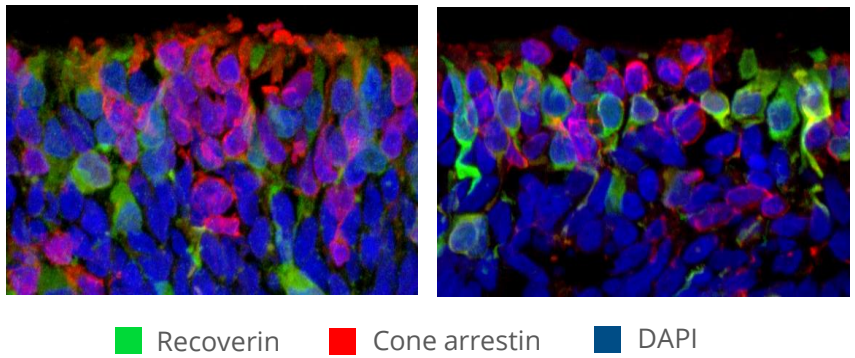
Cone-sparing makes LCA10 an ideal candidate for restorative RNA therapy

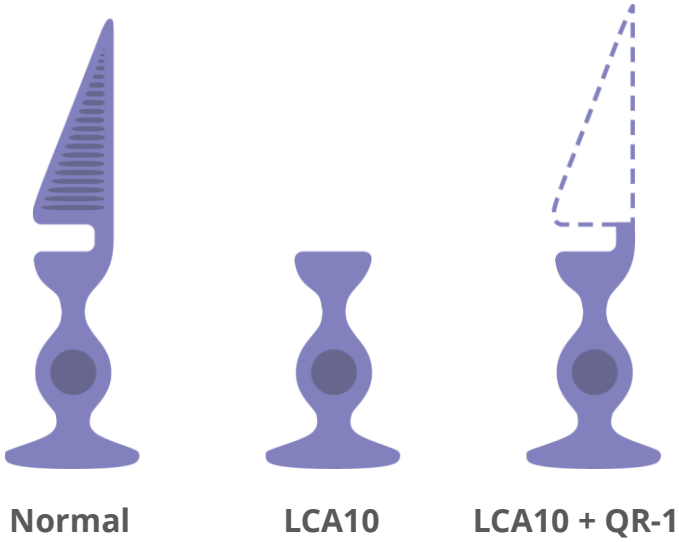




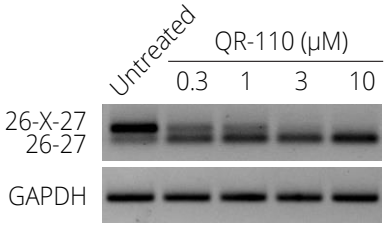
Retinal Organoid: QR-110-treated c.2991+1655A>G human LCA10 retinal organoids regrow cilium

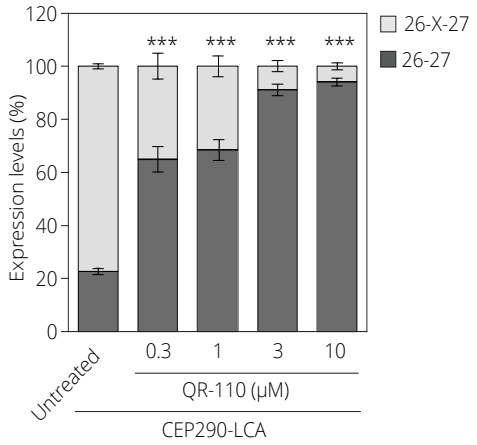
Differentiated retinal organoids

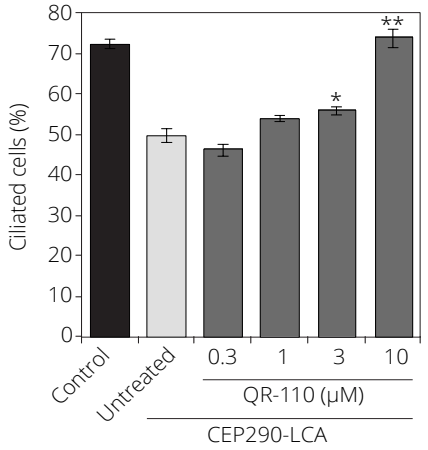


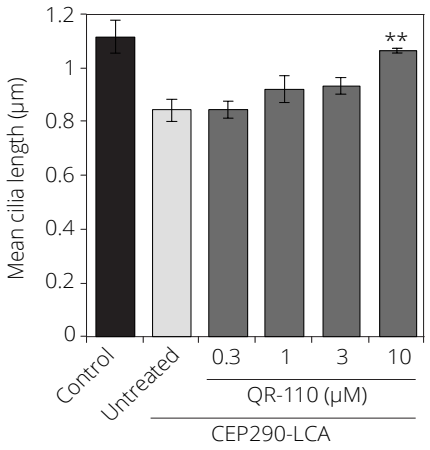


QR-110 corrects CEP290 mRNA



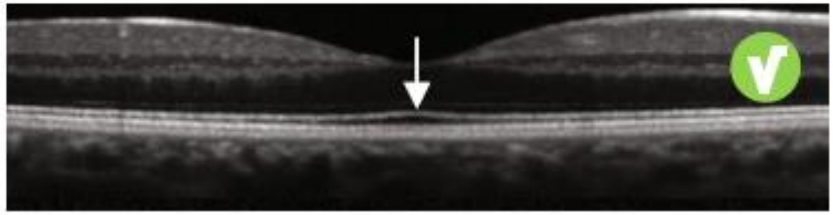






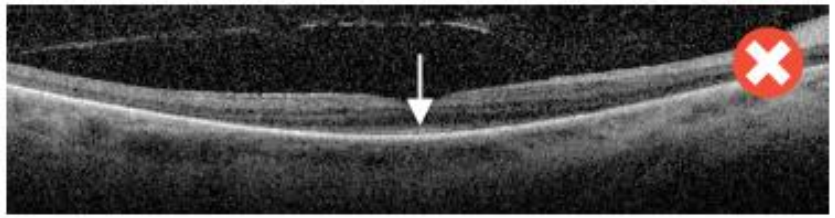
OCT imaging demonstrated regeneration of outer segment after sepofarsen treatment

Normal retina



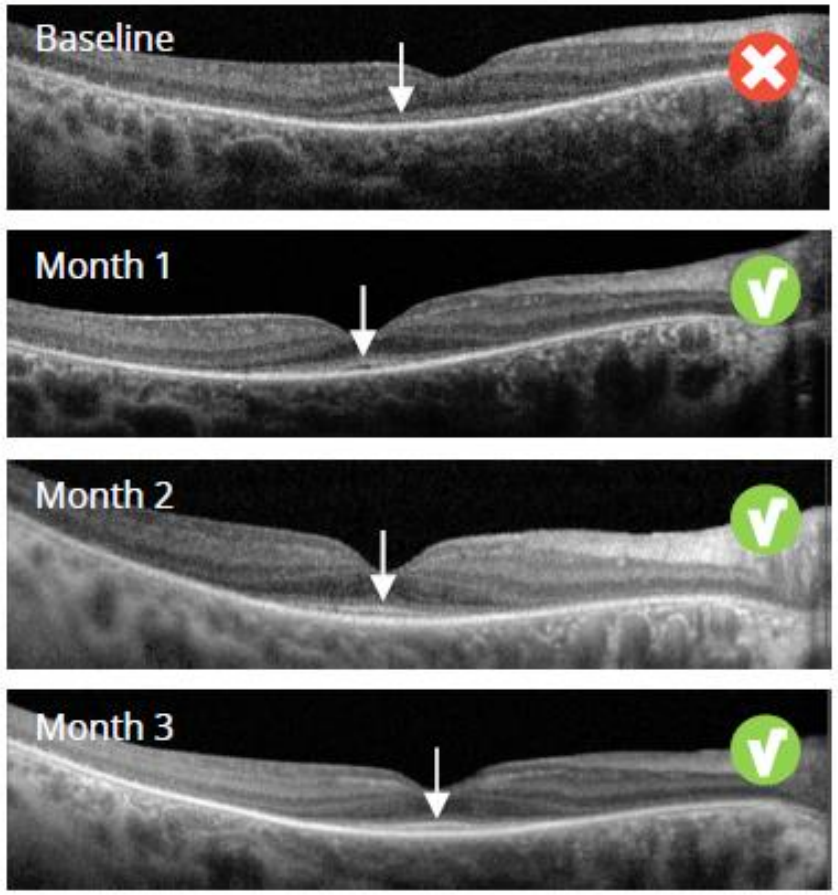
EZ line in normal retina shows outer segments by EZ-line, as detected by OCT

LCA10 retina



EZ line in missing in LCA10 retina due to lack of of outer segments

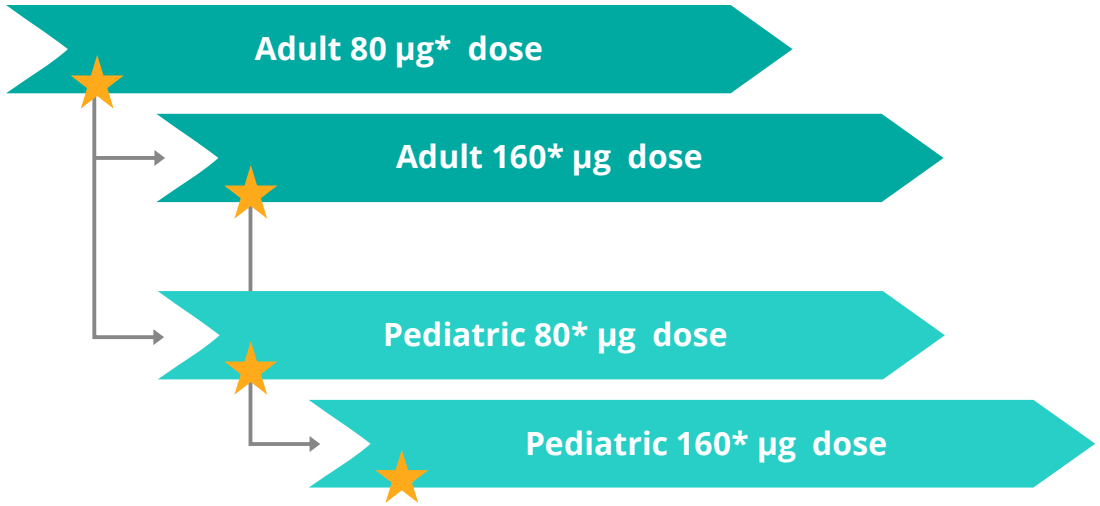
Restoration of EZ-line in subject



No change detected in untreated eye (data not shown)

Ongoing Phase 1/2 trial

Open label, multiple dose, dose escalation study, Phase 1/2



*Loading dose is double the maintenance dose

★ = DSMC review

- Enrolled eleven p.Cys998X LCA10 patients in range of 8-44 yo
- Intravitreal injections in one eye
- Participating sites: major sites in EU (UGhent) and US (UPenn, UIowa)
- Primary endpoints: Safety, tolerability
- Secondary endpoints and exploratory efficacy: Visual acuity, mobility course, FST, OCI, pharmacokinetics, OCT, PRO, ERG, pupilometry
- Orphan drug designation in EU and US
- FDA Fast-track designation

- 3 month positive interim analysis data reported in September 2018
  - >60% of patients improved on multiple efficacy endpoints
- Patients continue to be followed out to 12 months of treatment of which data is expected in H2 2019
- Eligible patients will be rolled over into an extension trial where they will be offered to also get their second eye treated

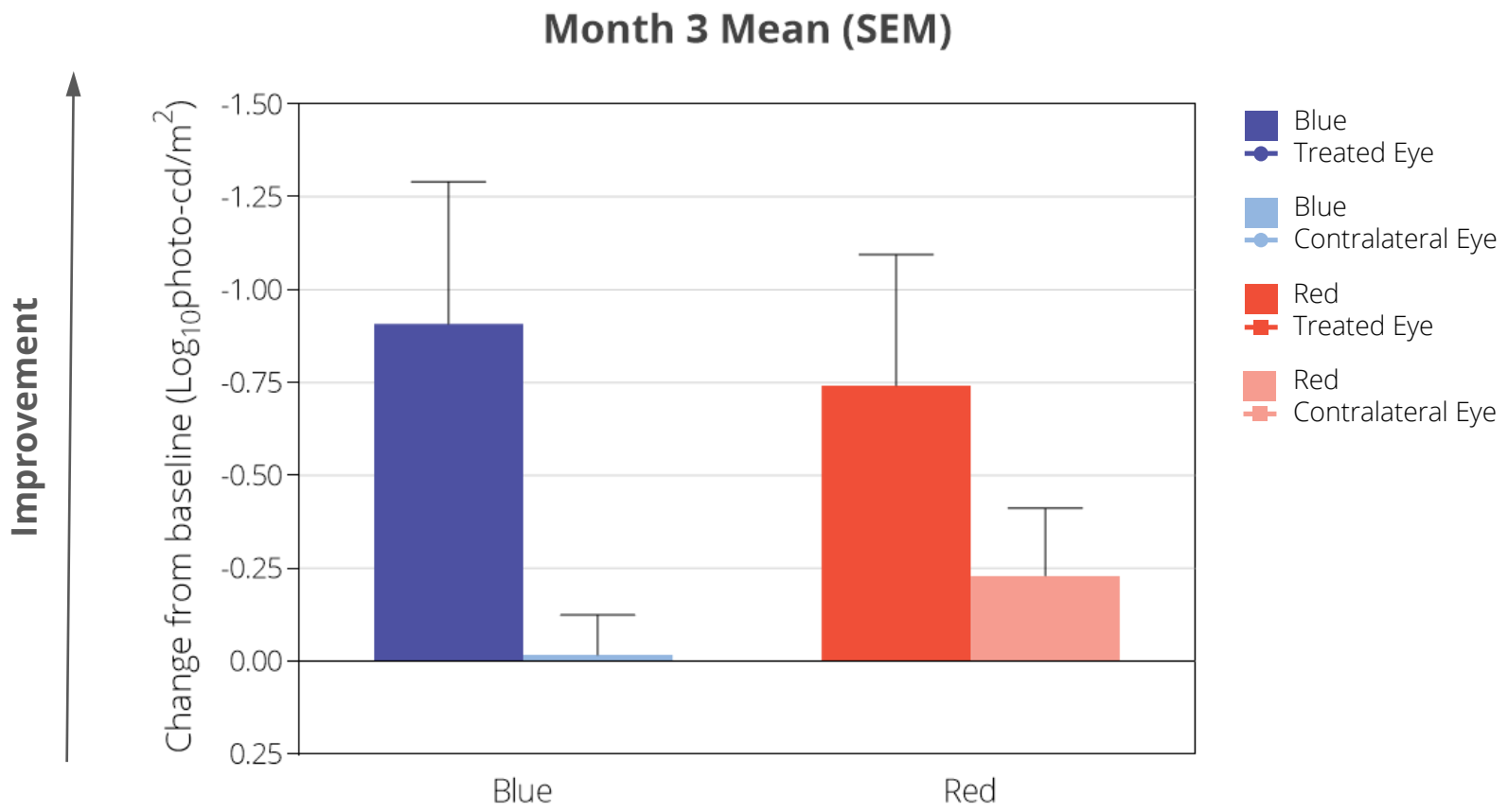
Top line efficacy results

Concordant improvement in all outcome measures

	Direction of improvement	Responder threshold	Change from baseline at Month 3 Mean (SEM)	
			Treated	Untreated
Visual Acuity (ETDRS/BRVT) – LogMAR (n=8)	↓= improved	≥ -0.3	-0.67 (0.32)	0.02 (0.05)
Mobility Course – level (n=7)	↑ = improved	≥2	2.57 (1.19)	1.36 (1.04)
Full field stimulus red (FST red) - cd/m2 (n=7)	↓= improved		-0.74 (0.35)	-0.23 (0.18)
Full field stimulus blue (FST blue) - cd/m2 (n=7)	↓= improved		-0.91 (0.38)	-0.02 (0.11)
Nystagmus tracking (OCI) - Log_{10}mm (n=7)	↓= improved		-0.14 (0.08)	-0.04 (0.06)

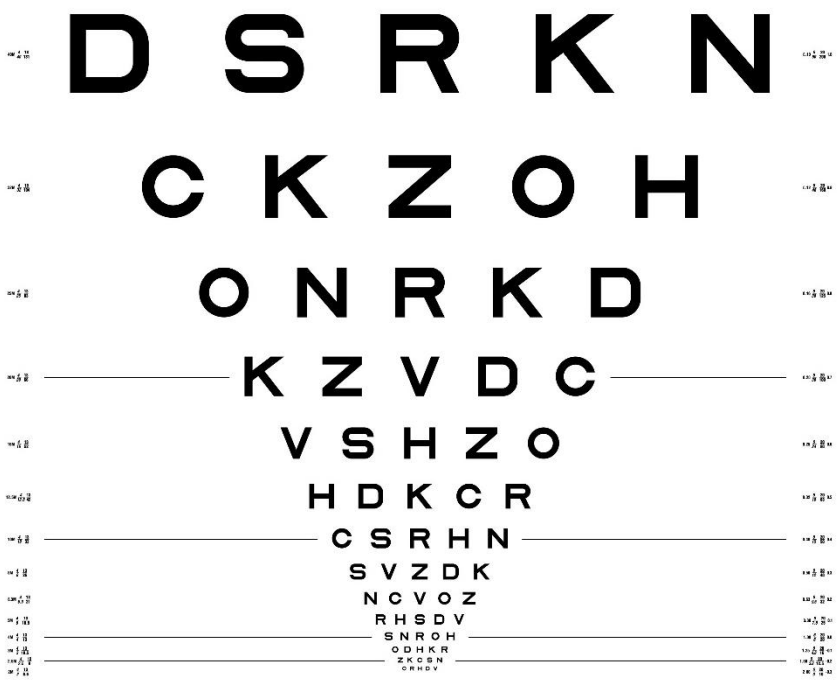
Full Field Stimulus Test (FST)

Measured with blue and red light

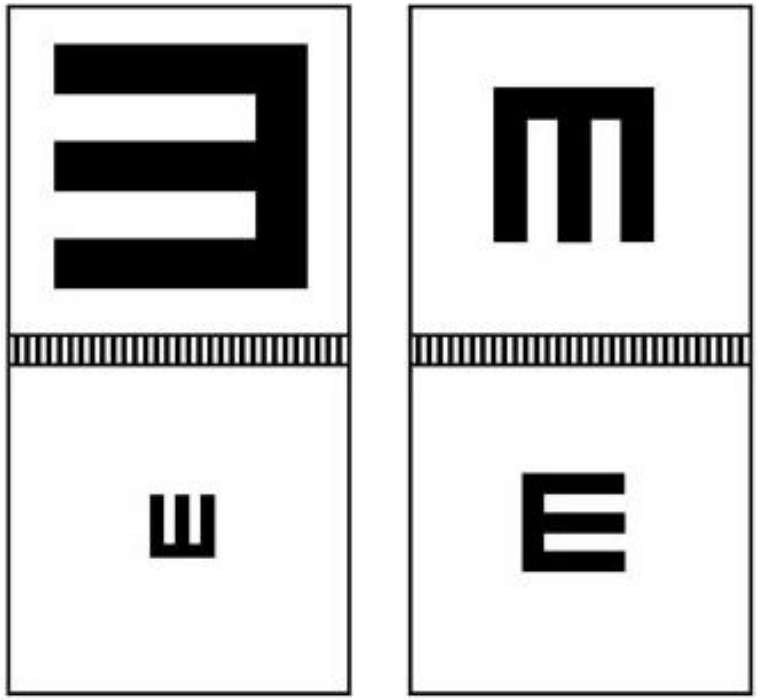


Best Corrected Visual Acuity (BCVA)

ETDRS
(LogMAR -0.3 - 1.6)

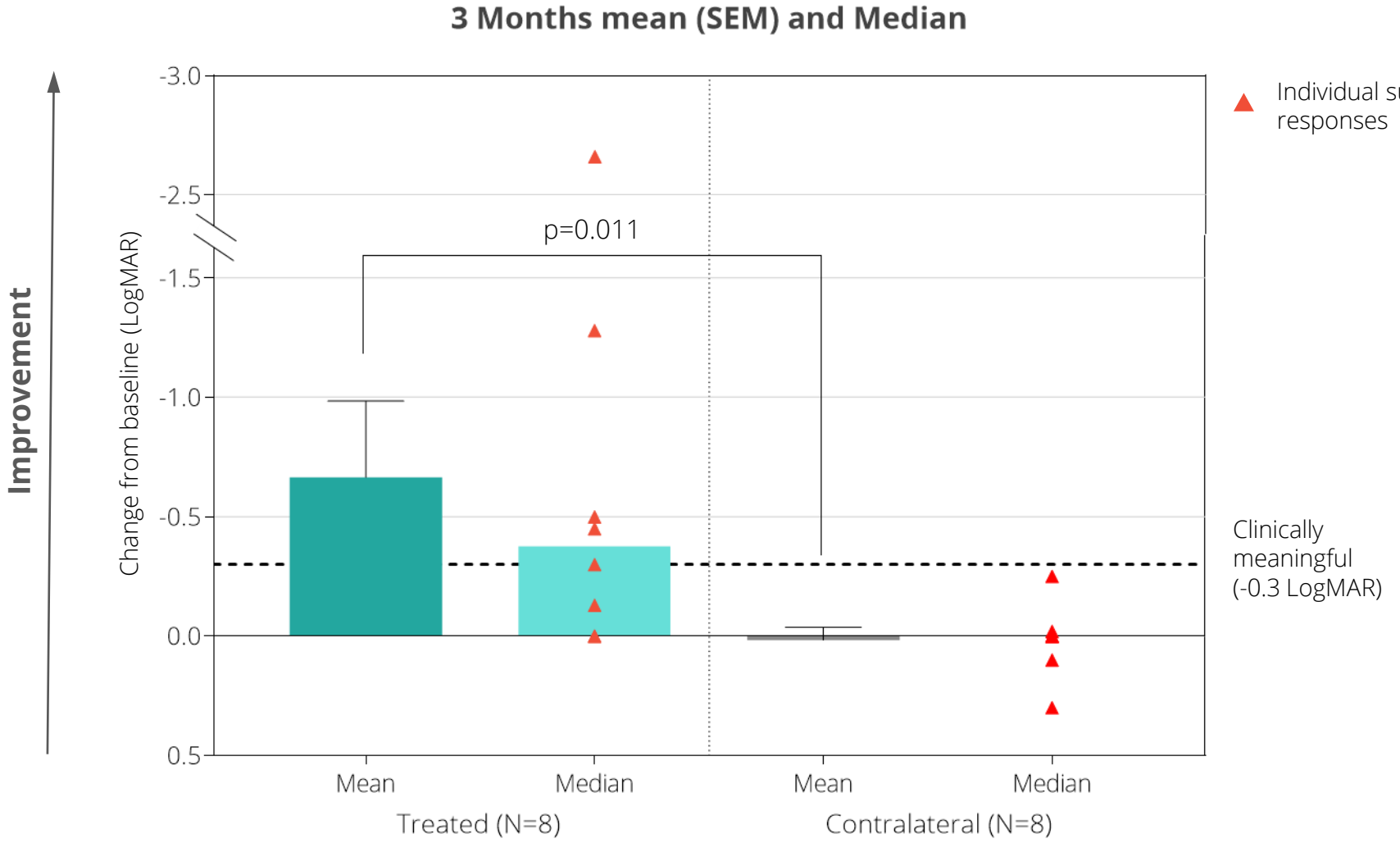


BRVT
(LogMAR 1.4 - 4.0)



Best Corrected Visual Acuity (BCVA)

Majority of subjects had clinically meaningful improvement

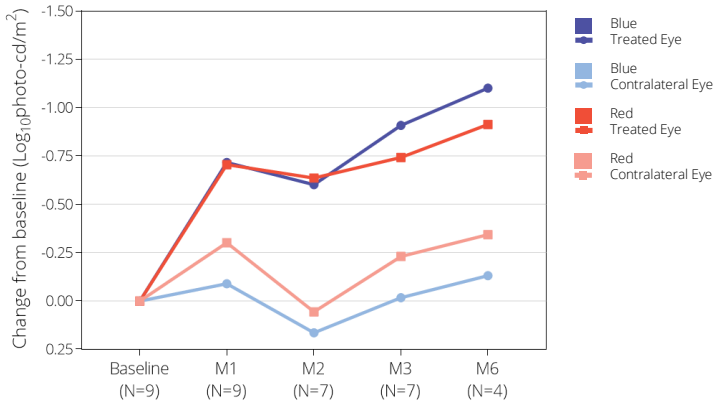


Sepofarsen time-to-onset of response was similar for FST and BCVA

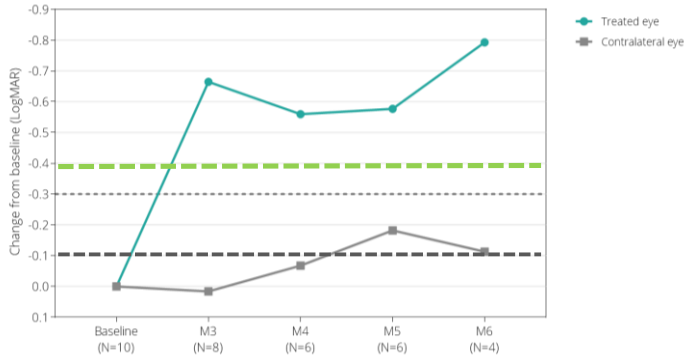
BCVA improvement appears to be more rapid than with Luxturna®

sepofarsen LCA10

FST

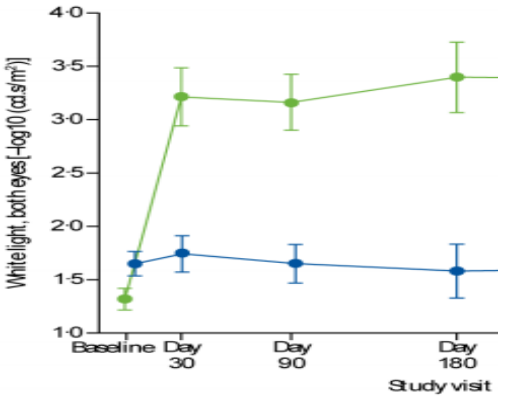


BCVA

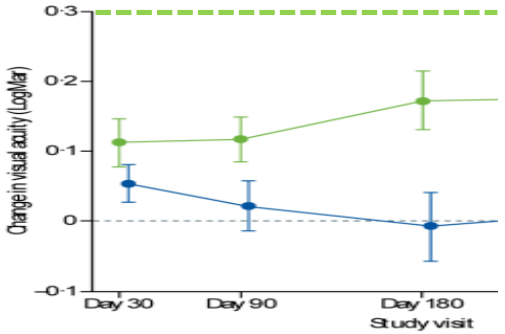


Luxturna® LCA2

FST



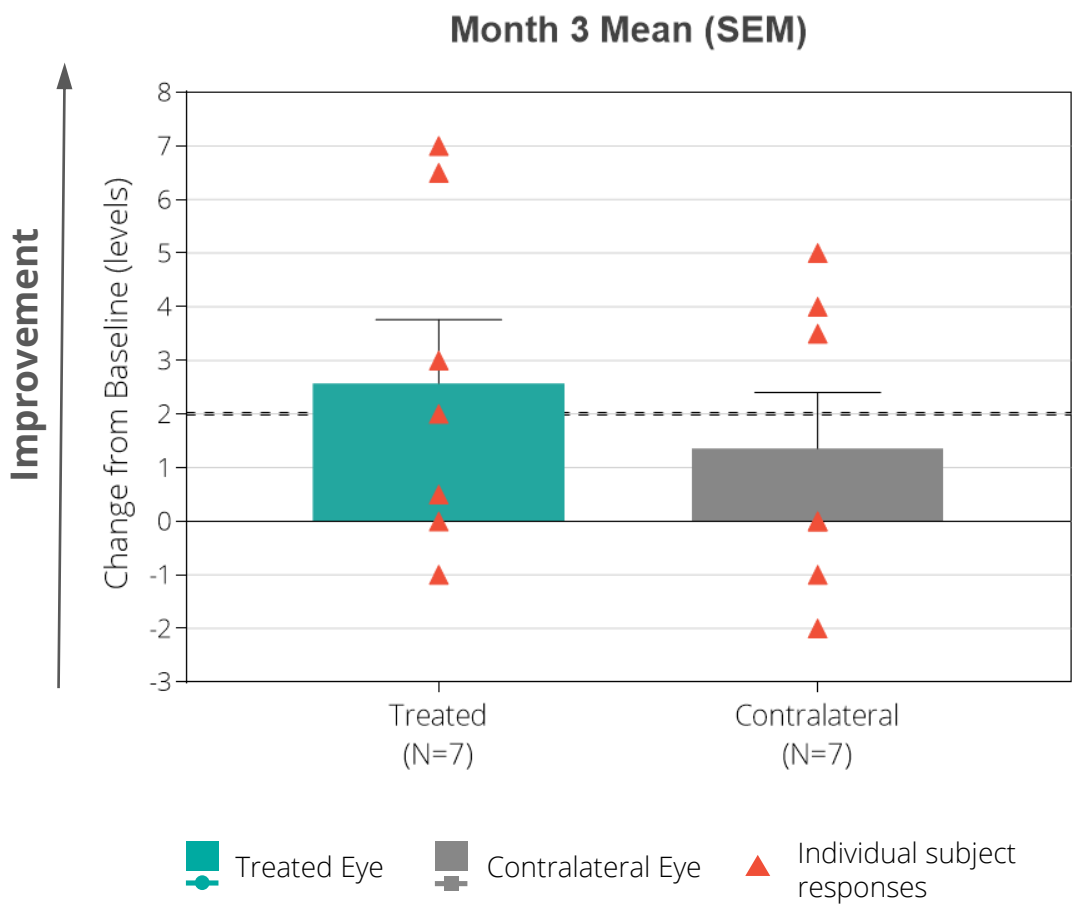
BCVA

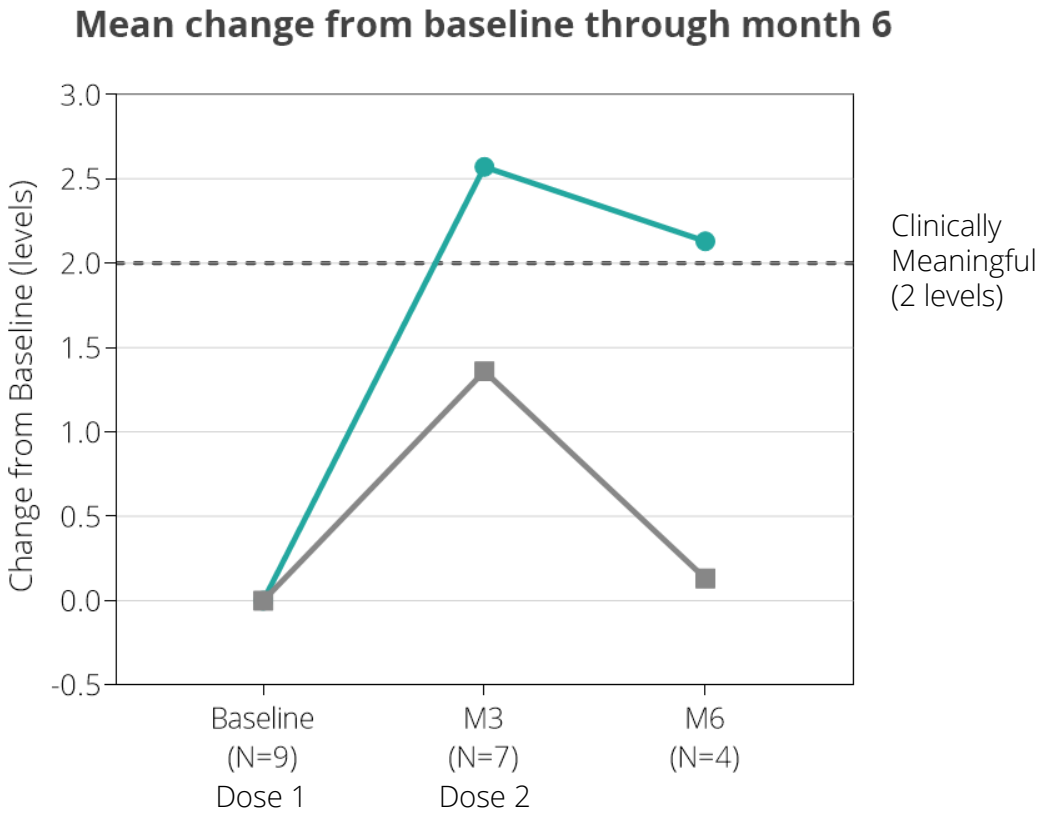


Modified from Lancet. 2017 August 26; 390(10097): 849–860.

Mobility course

Improved at month 3 and month 6





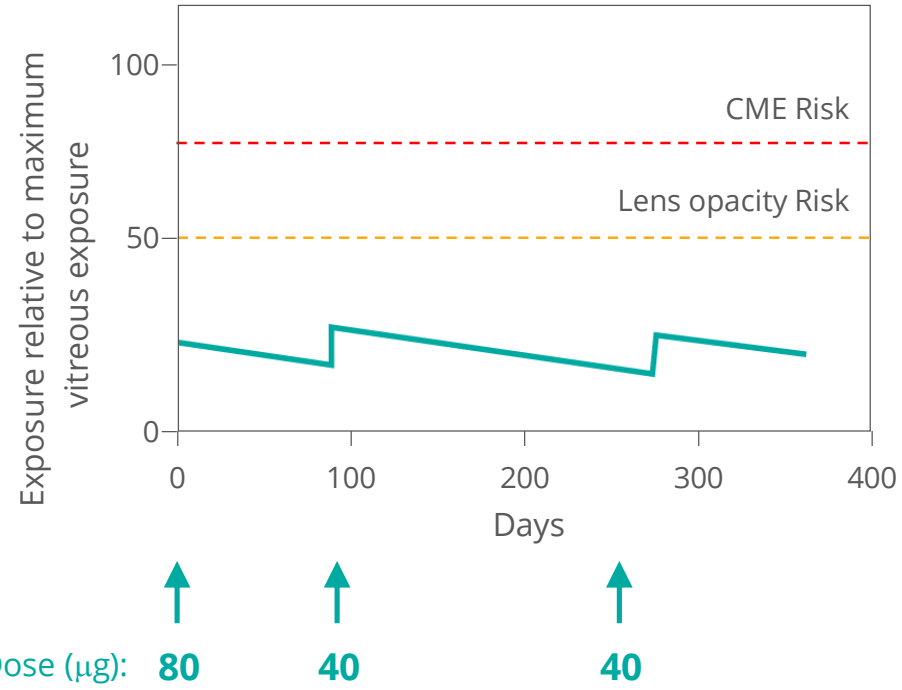
Discussion of evolving safety findings in trial PQ-110-001

- At the time of the IA, no significant, unanticipated AEs had been reported.
- Subsequently, lens opacities and CME were observed in a dose- and time-dependent manner:
  - Lens opacity occurred approx. 4 months earlier in mid dose group compared to low dose group, with none observed prior to month 4;
  - CME only observed in mid dose group (3-4 months into the study)
- Investigators judged that 3 of 6 lens opacities required surgical removal
  - 2 subjects had demonstrated improved BCVA prior to developing the cataract. After surgery restoration of benefit was observed.
- Both subjects with CME were judged to be mild in severity and not associated with reduced visual acuity.
  - Both started on standard of care treatment with partial resolution noted on one month follow-up OCT
- Dose modifications and longer dosing interval introduced in program:
  - After 12 month visit, all subjects will be rolled over into an extension trial with every six month treatment with the low dose regimen.

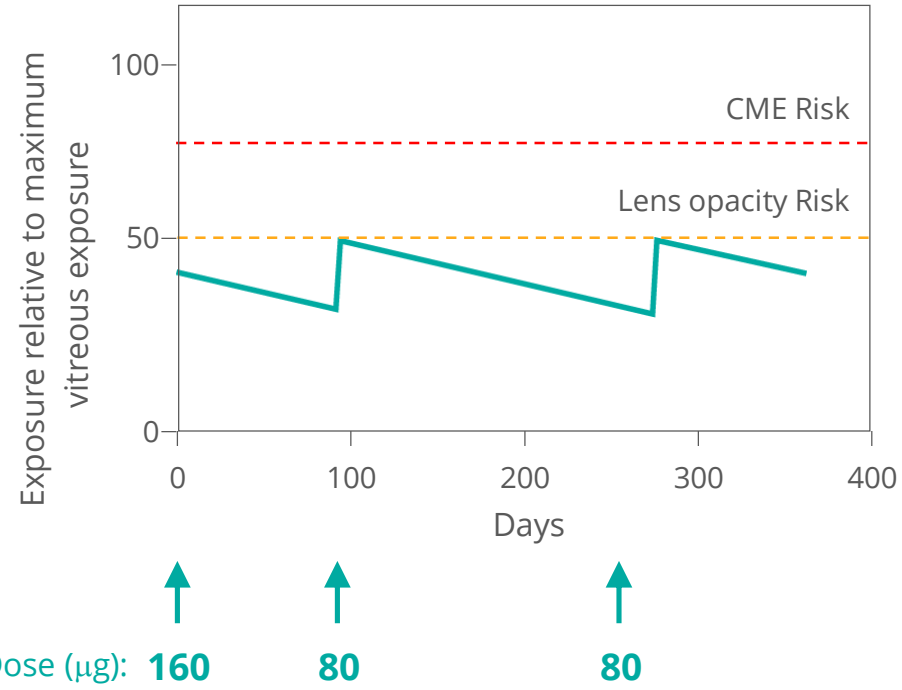
Study PQ-110-003 proposed dose regimens

Modeling based on estimated $t_{1/2}$ in retina 200d from NHP

Low dose pivotal
(80 μg load/40 μg maintenance*)



Primary dose pivotal
(160 μg load/80 μg maintenance*)



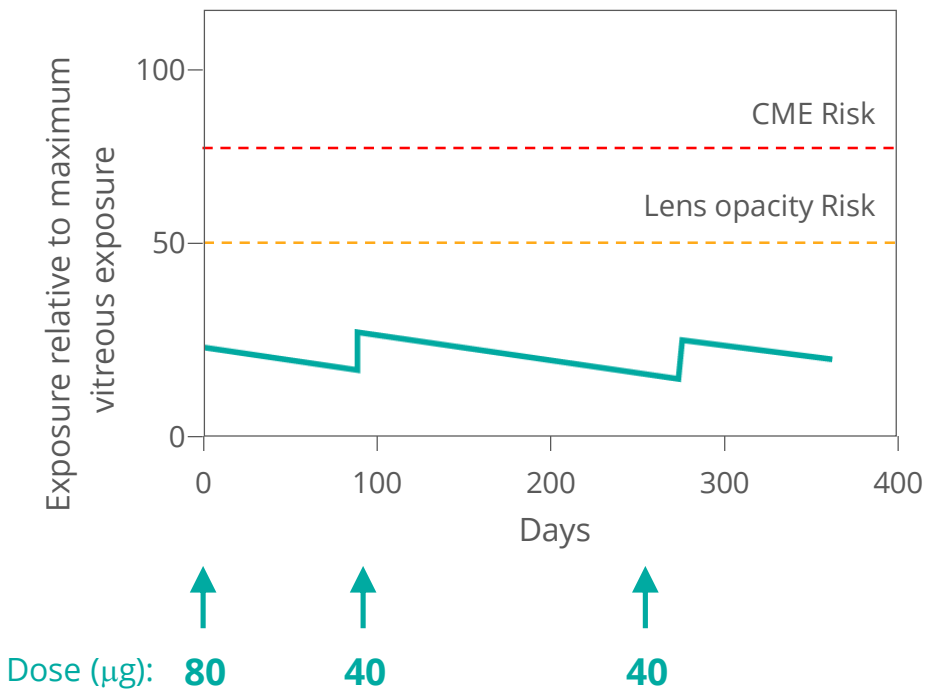
**Every 6 months after 3 month dose*

— Projected human tissue exposure (200d $t_{1/2}$)

Study PQ-110-003 proposed dose regimens

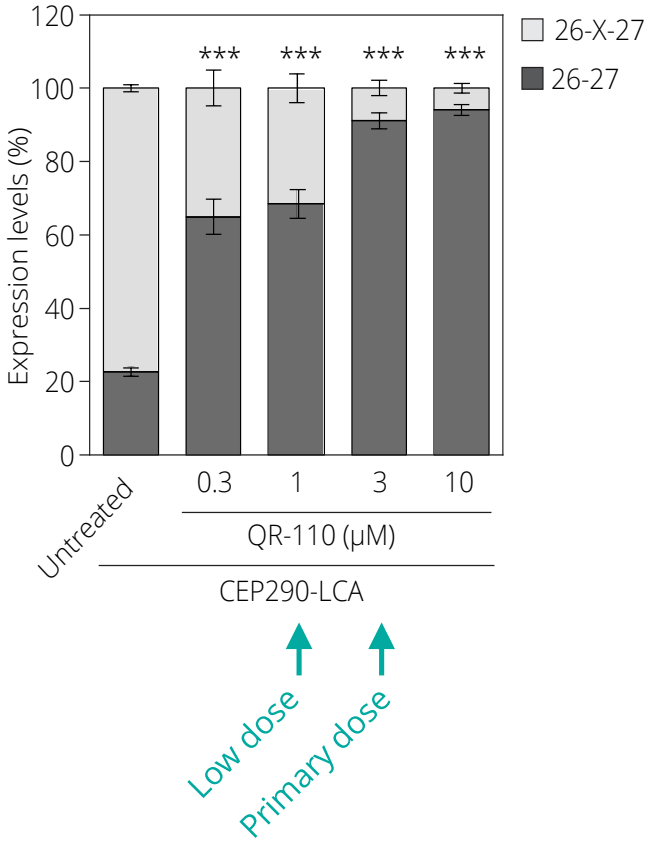
Efficacy is predicted in low dose regimen

Low dose pivotal
(80 μg load/40 μg maintenance*)



**Every 6 months after 3 month dose*

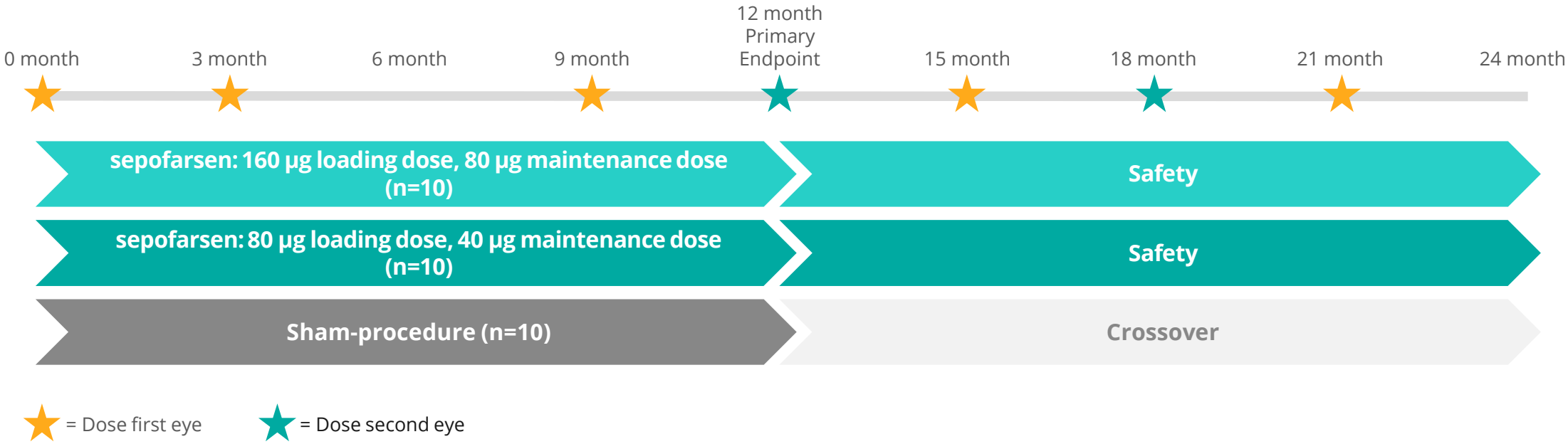
CEP290 exon skipping in organoid



Pivotal Phase 2/3 trial

Design agreed on with FDA

Illuminate



- Double-masked, randomized, controlled, 12-month, multiple dose study
- Could serve as the sole registration trial
- Sites in North America and select EU countries

- 30+ patients >8 years old
- Multiple IVT injections in both eyes
- Expected to start H1 2019
- Primary (registration) endpoint:
  - Visual acuity (ETDRS, BRVT)

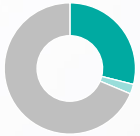
- Key secondary endpoints
  - Mobility course
  - Full field stimulus testing (FST)
  - Ocular instability (OCI)
  - Optical coherence tomography (OCT)

QR-421a for Usher syndrome

Designed to treat genetic vision loss in Usher and non-syndromic RP

Usher

Develop hearing and vision loss in childhood and are completely blind by mid adulthood



USH2A exon 13 mutations affect **~16,000** patients in Western world

Partnership

FOUNDATION FIGHTING BLINDNESS

Awarded $7.5M financial support from FFB to conduct trial

Unmet need

For ***USH2A* exon 13** no therapy available

- ✓ RNA is established modality in eye
- ✓ Strong preclinical proof of concept in patient retinal model
- ✓ Orphan drug designation
- ✓ Fast track designation
- ✓ IND approved by FDA

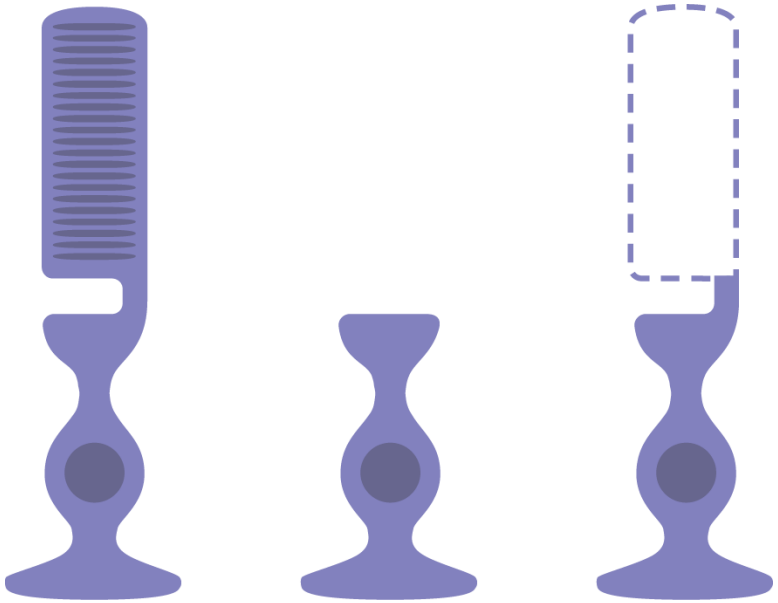
STELLAR Phase 1/2 trial

- Expect to dose a first patient with QR-421a in Q1 2019 with safety and efficacy results in mid-2019
- Expect results from multiple dose adaptive trial YE 2020

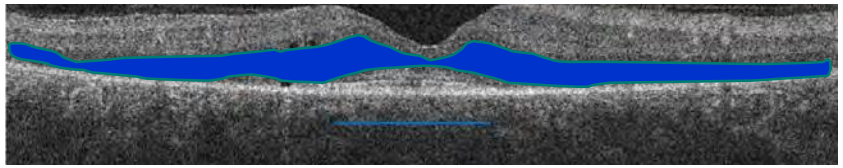
Molecular rationale is similar in Ush2a and LCA10

QR-421a primarily targets rod restoration

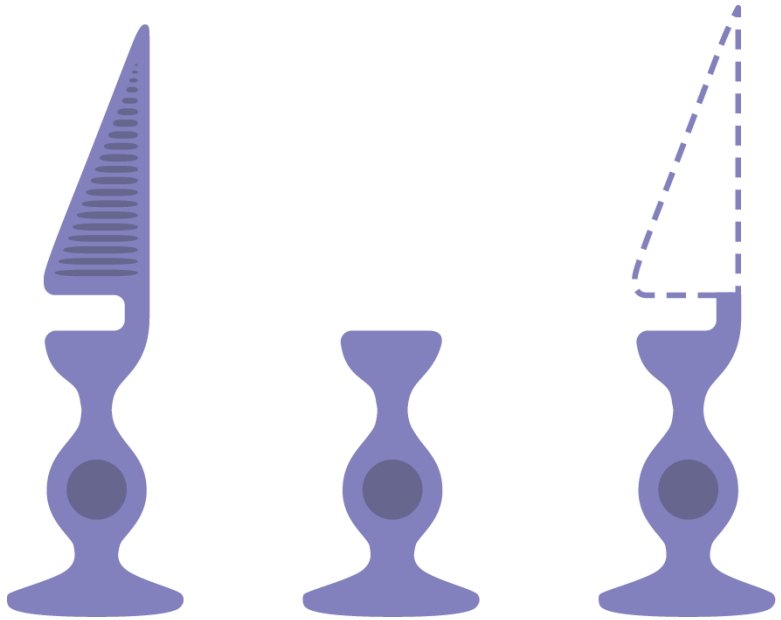
Ush2a



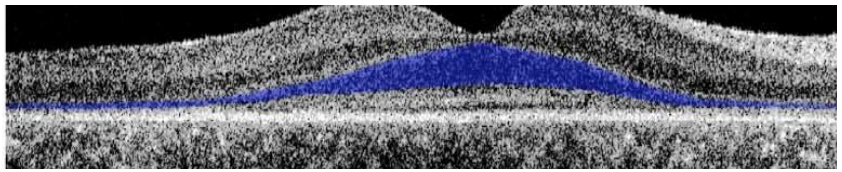
Normal | Ush2a | Ush2a + **QR-421a**



LCA10



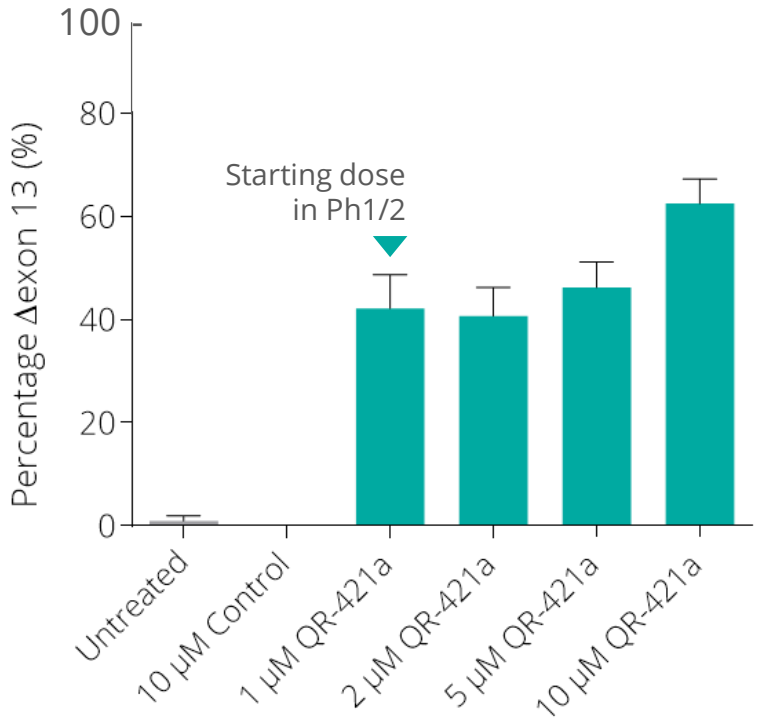
Normal | LCA10 | LCA10 + **sepofarsen**



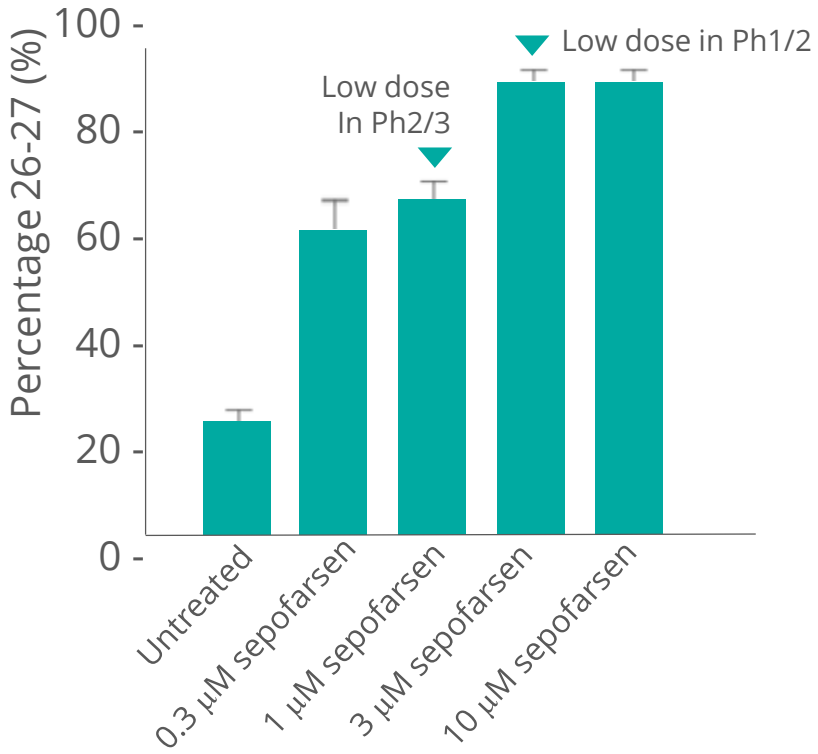
Similar retinal organoid molecular activity of QR-421a and sepofarsen

Lower starting dose in QR-421a Phase 1/2 program

QR-421a-treated optic cups
From Usherin c.2299delG homozygous patient

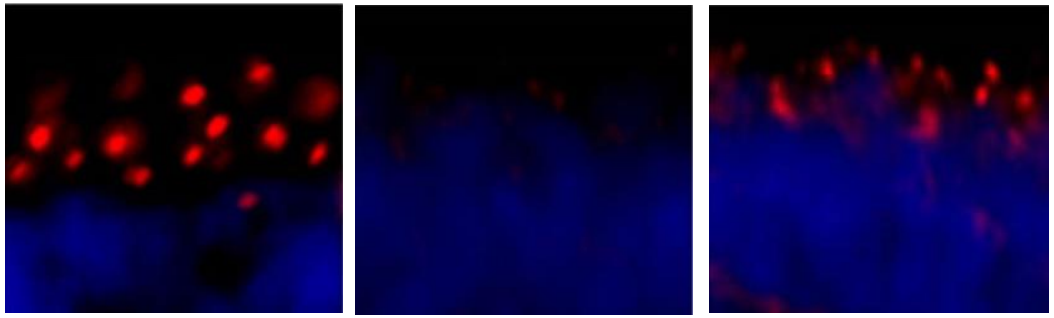


Sepofarsen-treated optic cups
From CEP290 c.2991+1655A>G homozygous patient

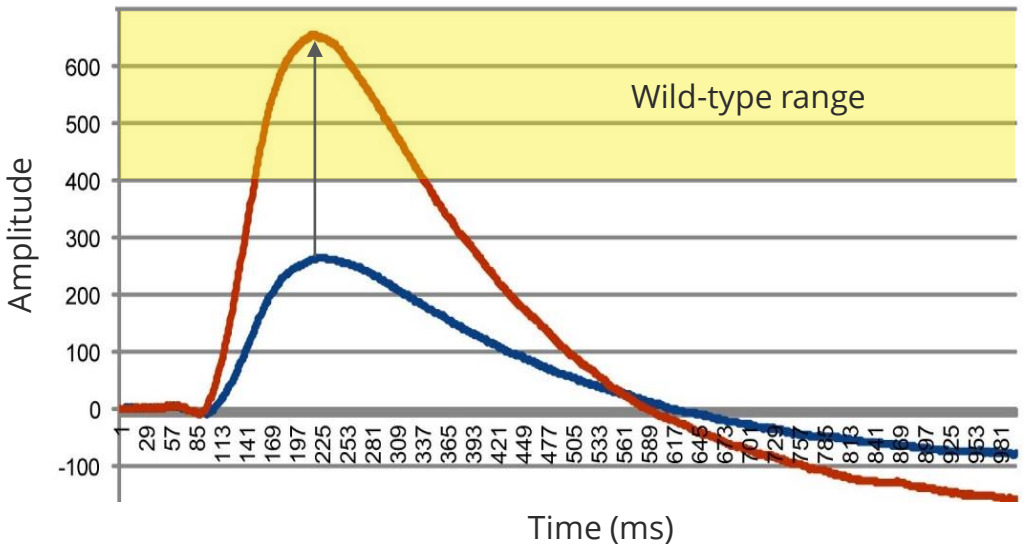


Restoration of usherin protein and ERG amplitude in exon 13 mutant zebrafish

Usherin protein (in red) in zebrafish retina



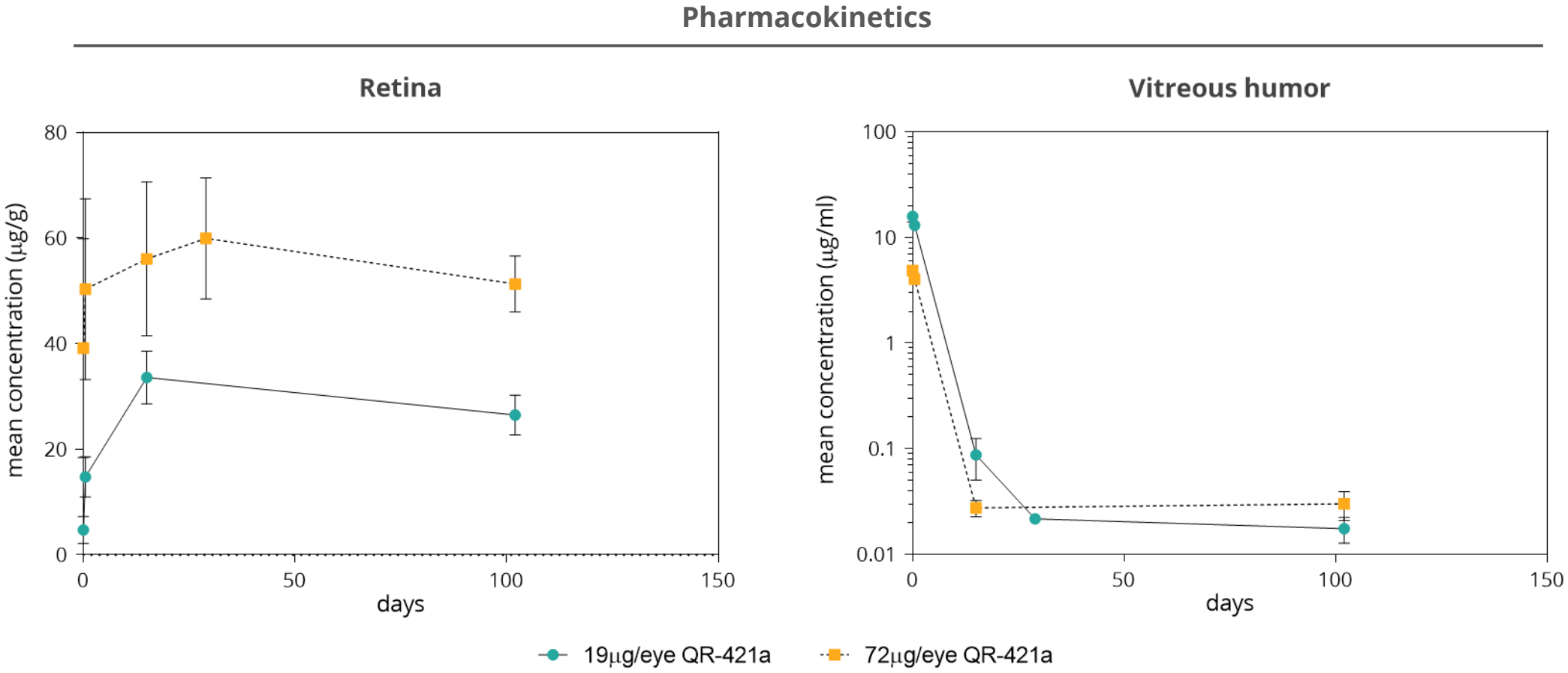
ERG with light stimulus in zebrafish



Erwin van Wijk, Radboudumc, Nijmegen, the Netherlands

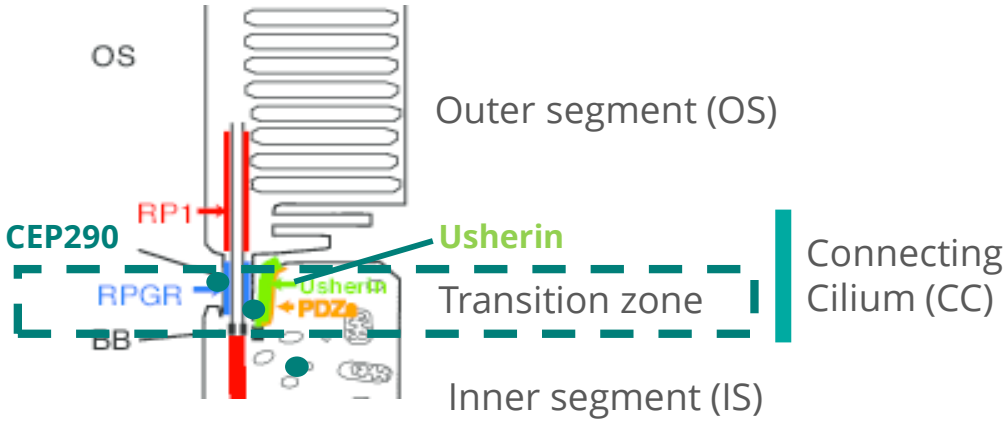
Pharmacokinetics in non human primates

Rapid clearance from vitreous with prolonged retention and activity in retina



“Read-through” from LCA10 to Ush2a

- CEP290 and Usherin are co-localized in photoreceptors
- Sepofarsen and QR-421a have similar concentration-response curves in retinal organoids
- QR-421a has additional preclinical translational PoC in animal model



Candidate	Cellular MoA	Target cell	Active in retinal organoid	Active in animals	Active in humans
sepofarsen	Restore cilium and OS	Photoreceptor Cones	Yes ≤1μM	Unknown	Yes
QR-421a	Restore cilium and OS	Photoreceptor Rods	Yes ≤1μM	Yes	TBD

Key trial goals/objectives

- Establish safety and pharmacokinetics
- Identify dose/duration for next study
- Assess efficacy based on:
  - Improvement in visual fields, particularly rod function
  - Evidence of structural improvement consistent with VF improvement as measured by OCT
  - Other functional vision improvements

Usher Syndrome clinical disease progression

Hearing impairment

Loss of visual field (rod degeneration)

Complete blindness (rods and cones degenerated)

AGE* (YEARS) 0 10 20 30 40 50 60

*High within patient variability in onset and progression of disease

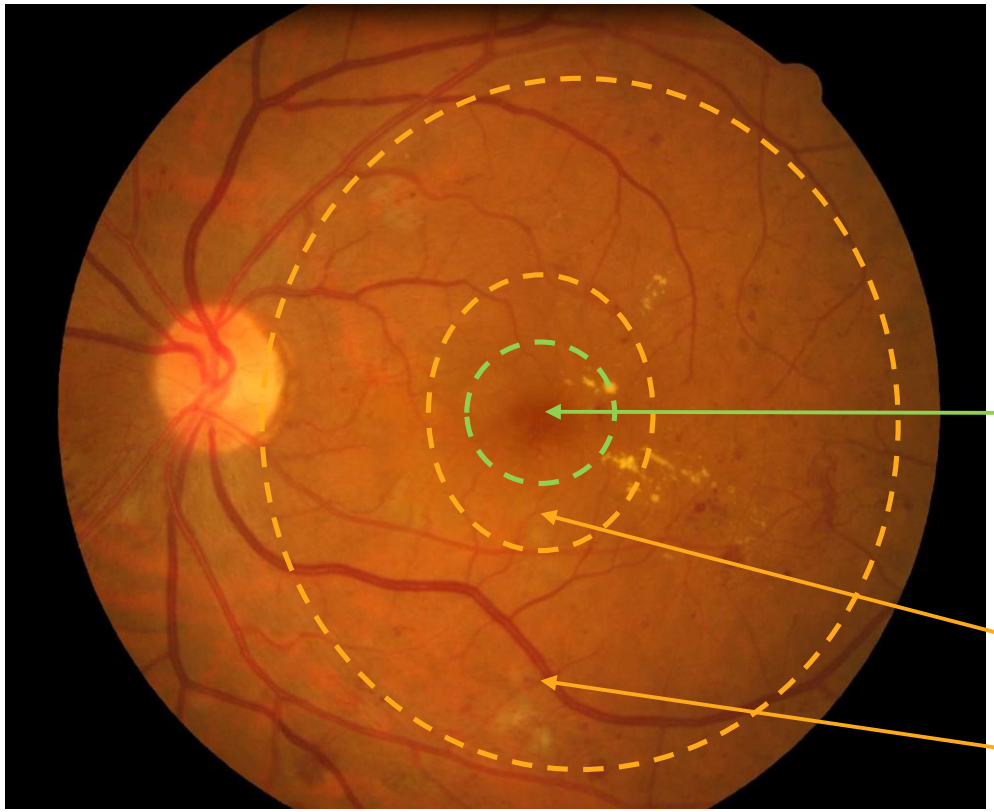
Night blindness (start rod degeneration)

Loss of central vision (cone degeneration)

Initial study population (FIH)

Expanded study population (Ph2/3)

Area of recoverable function in Ush2a localized by OCT in early and advanced disease

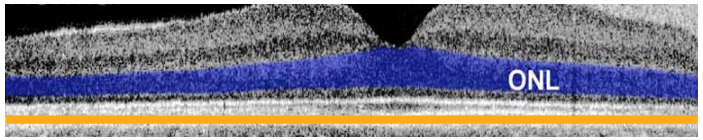


Macula

Peripheral
Advanced

Peripheral
Early

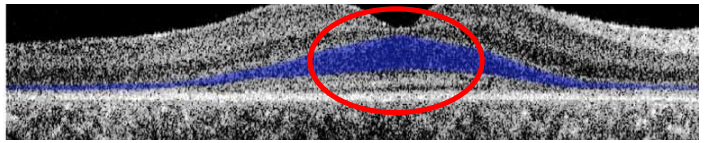
Normal



Normal EZ

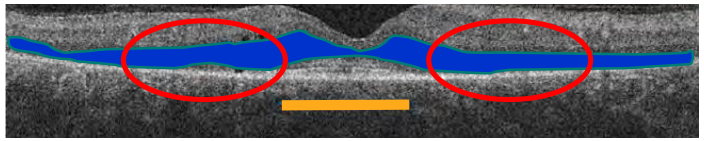
Peripheral | Macula | Peripheral

LCA10



No EZ

Ush2a

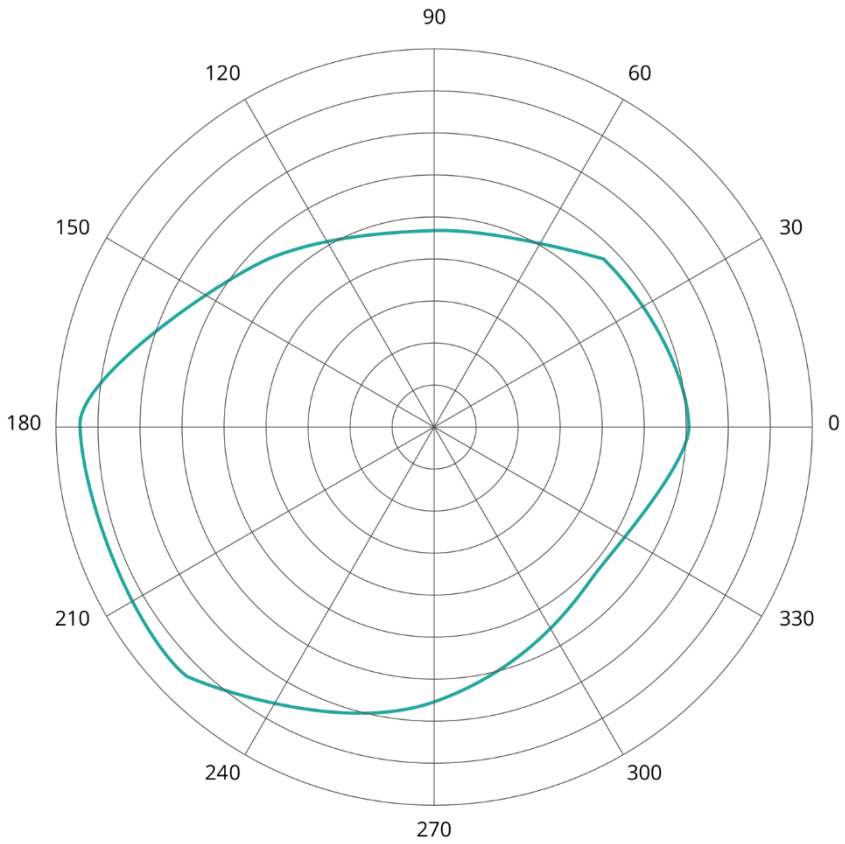


Macula EZ only

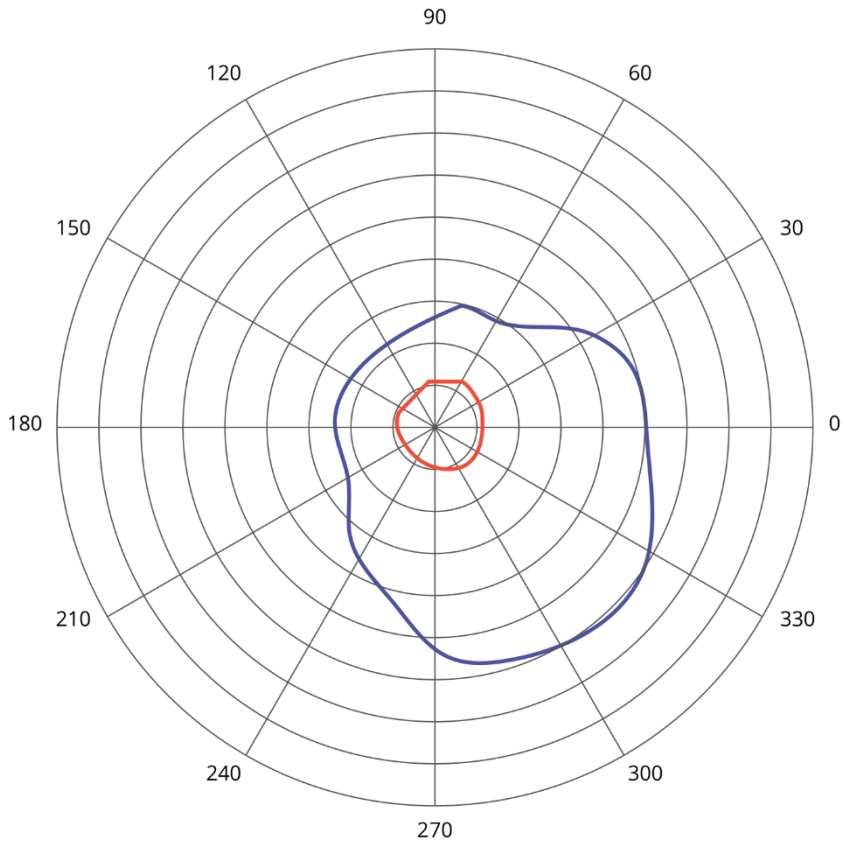
= Area of potential recovery

Visual field defects

Normal Visual Field



Usher syndrome

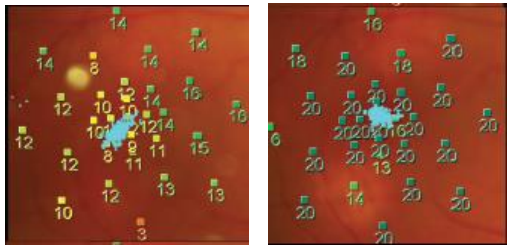


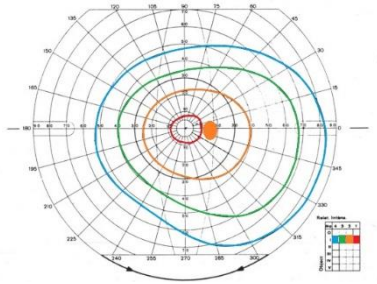
Earlier stage disease

Later stage disease

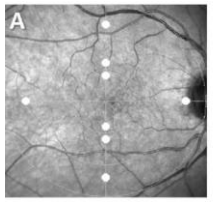
Primary efficacy measures:

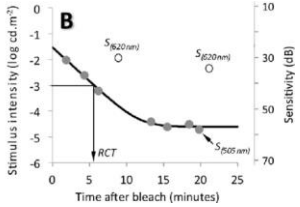
Quantifying visual field defects and EZ-line extension





Automated perimetry

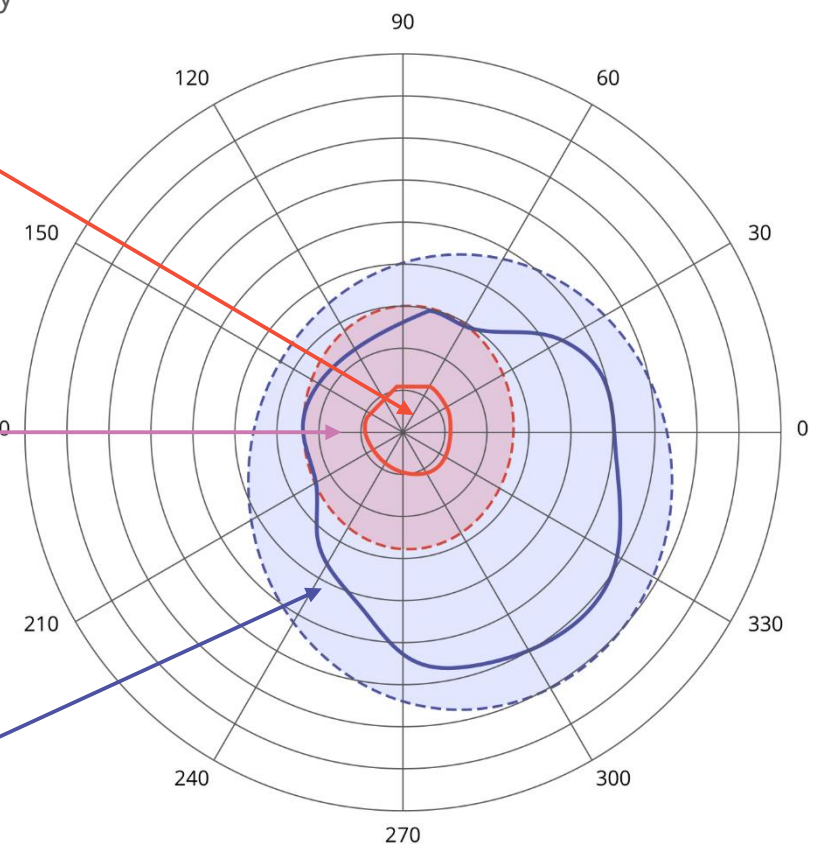




Microperimetry

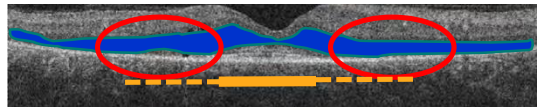
Dark-adapted chromatic perimetry

Usher syndrome



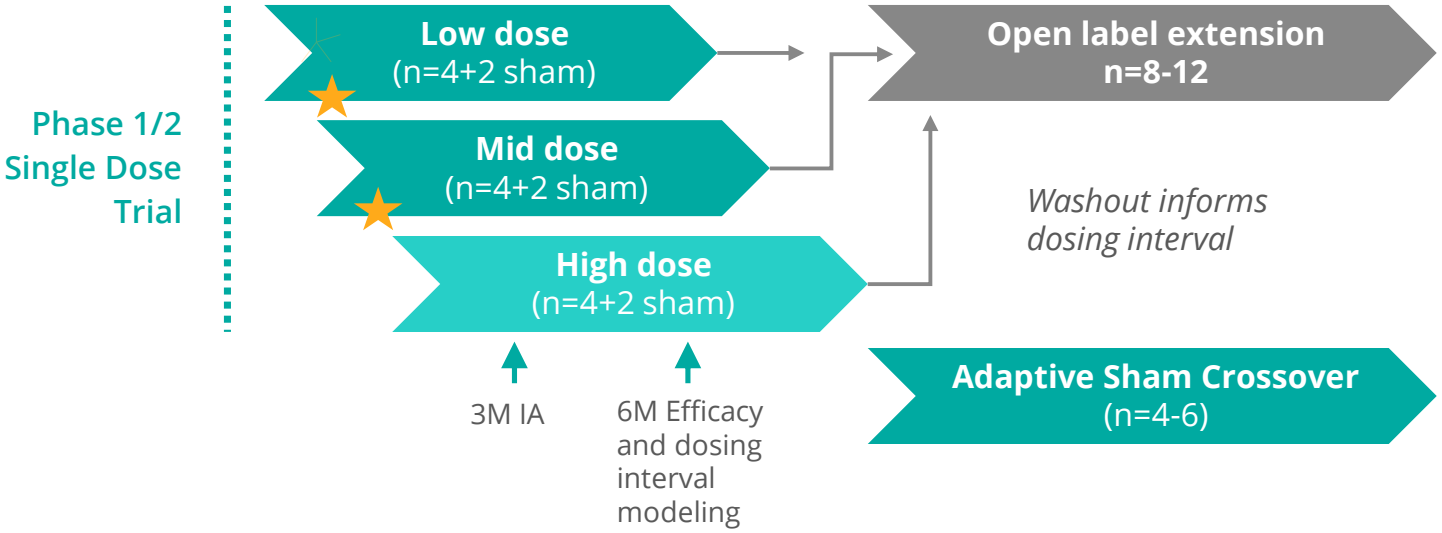
- Earlier stage disease
- Later stage disease
- Potentially viable photo-receptors as shown by OCT Indicates potential area of visual functional restoration by QR-421a

OCT: Extension of EZ Change in ellipsoid zone



Macula EZ plus peripheral extension

QR-421a Phase 1/2 trial in Usher 2a patients



STELLAR

★ Meeting of independent DSMC

STELLAR Phase 1/2 trial

- Single dose, double-masked, randomized, controlled trial
- Goals include safety and efficacy PoC and dose interval
- ~18 adult patients with moderate to severe eye disease
- Inclusion criteria: visual field of >10°, visual acuity of 20/32 or worse

Single intravitreal injection in one eye, or sham treatment (randomized 2:1 active:control per cohort)

- Key trial endpoints: Visual field (Medmont DAC Perimetry, Static VF, microperimetry) and OCT
- IND open, data expected in mid-2019

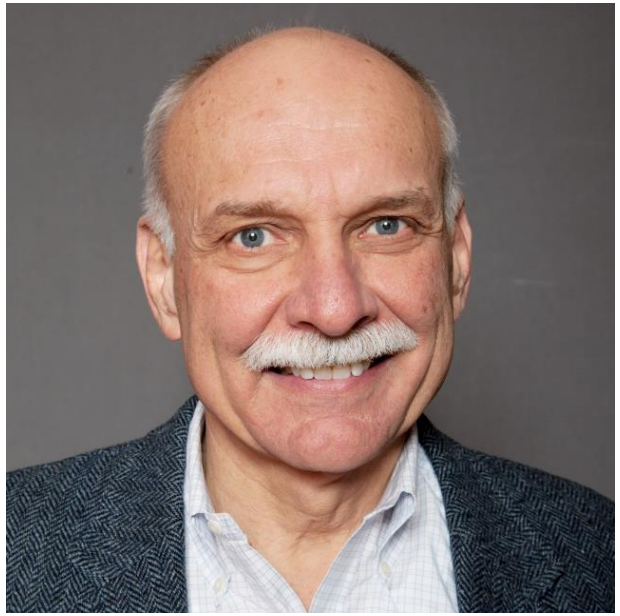
Q&A

ProQR®

Break

Presentations to start again at 10am ET

Thaddeus (Ted) Dryja, MD



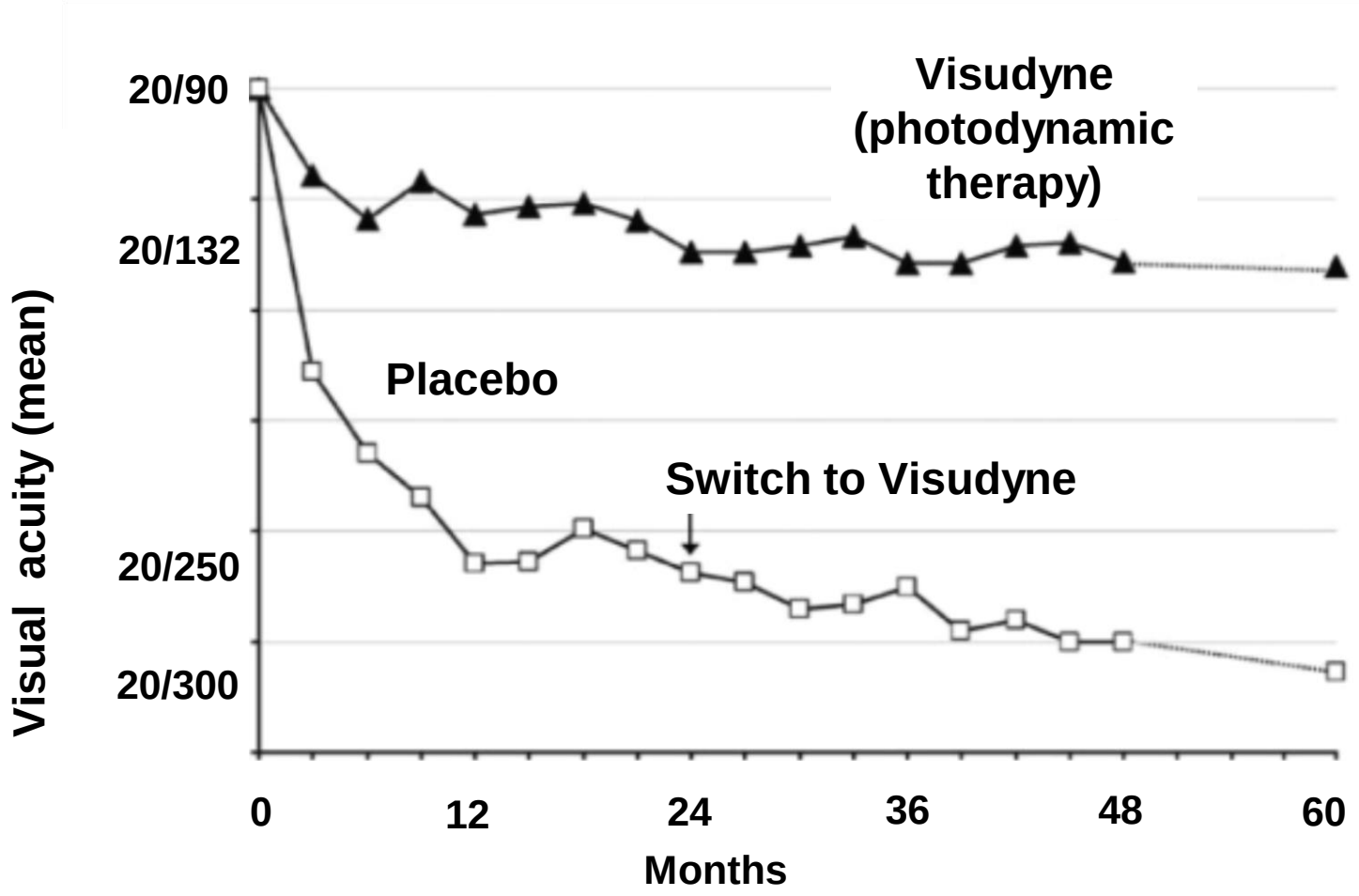
- **Professor of Ophthalmology** at **Harvard** Medical School and at the **Massachusetts Eye and Ear** Infirmary
- Previously **Global Head of Ophthalmology Research** at the **Novartis** Institutes for Biomedical Research
- Research in **molecular genetics** of hereditary diseases of the retina
- **Research discoveries** include the identification the genes responsible for forms of **retinal degeneration and dysfunction**
- Member of the **U.S. National Academy of Sciences**

Therapeutic History of Ophthalmology

Thaddeus (Ted) Dryja, *MD*

Professor of Ophthalmology Harvard Medical School, Faculty member at the Massachusetts Eye and Ear Infirmary

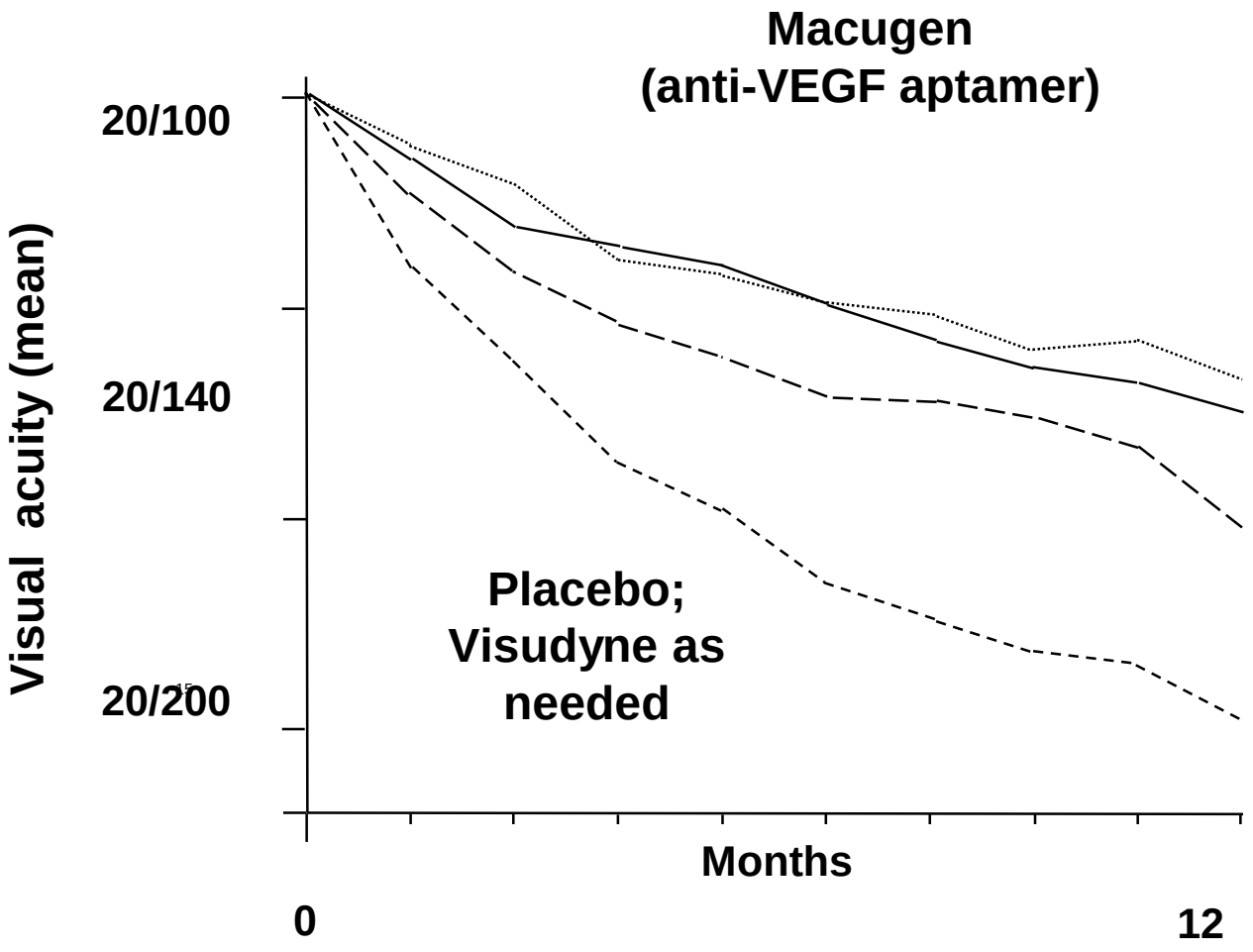
2000: First therapy for neovascular age-related macular degeneration started a multi-billion-dollar company (QLT)



Visudyne: a photosensitizing dye is given intravenously and a laser photocoagulates the abnormal vessels

Kaiser PK et al., Graefe's Arch Clin Exp Ophthalmol 244:1132-1143, 2006

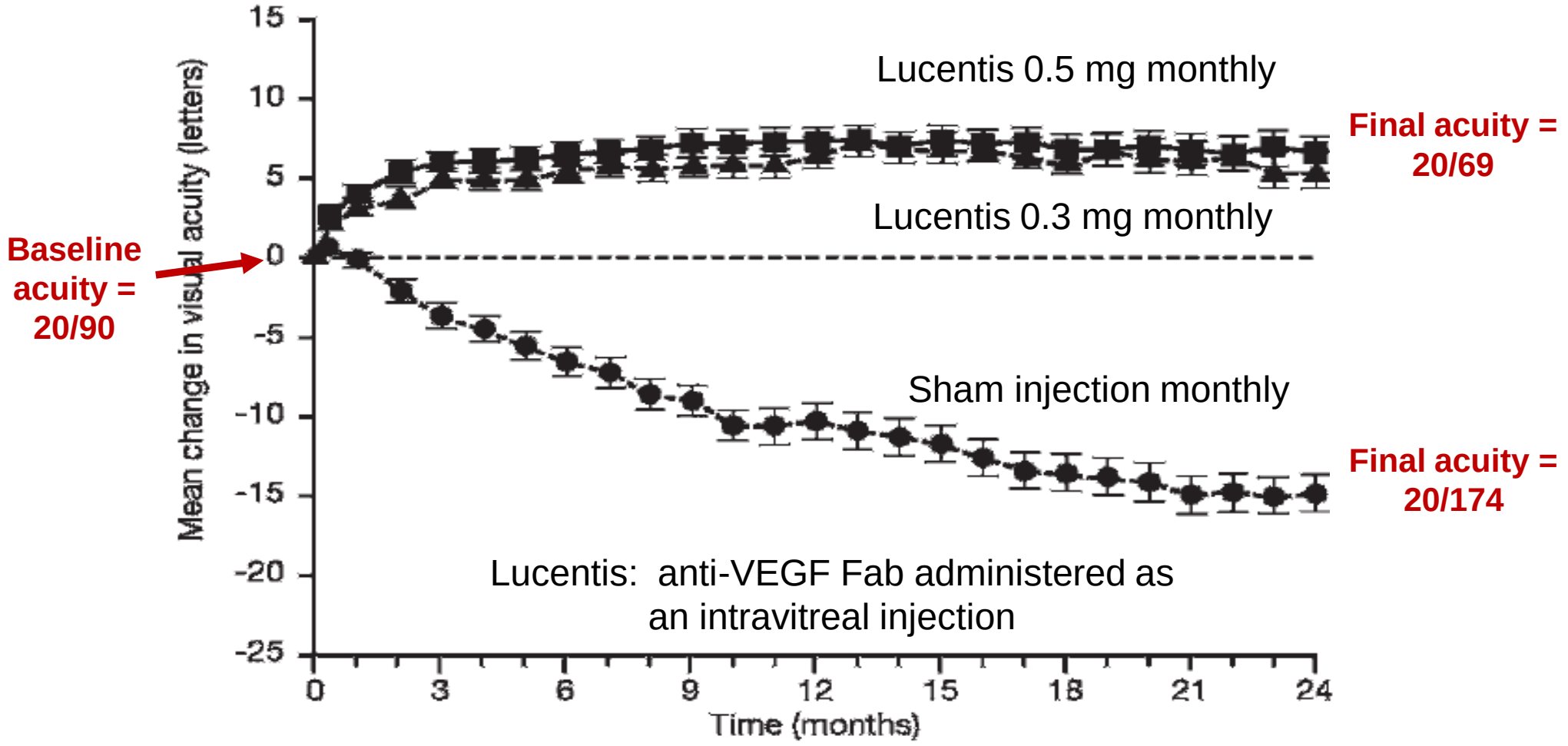
2004: Second therapy for neovascular age-related macular degeneration started another multi-billion-dollar company (Eyetech)



Macugen injections given every 6 weeks

Gragoudas et al., N Engl J Med 351:2805-2816, 2004

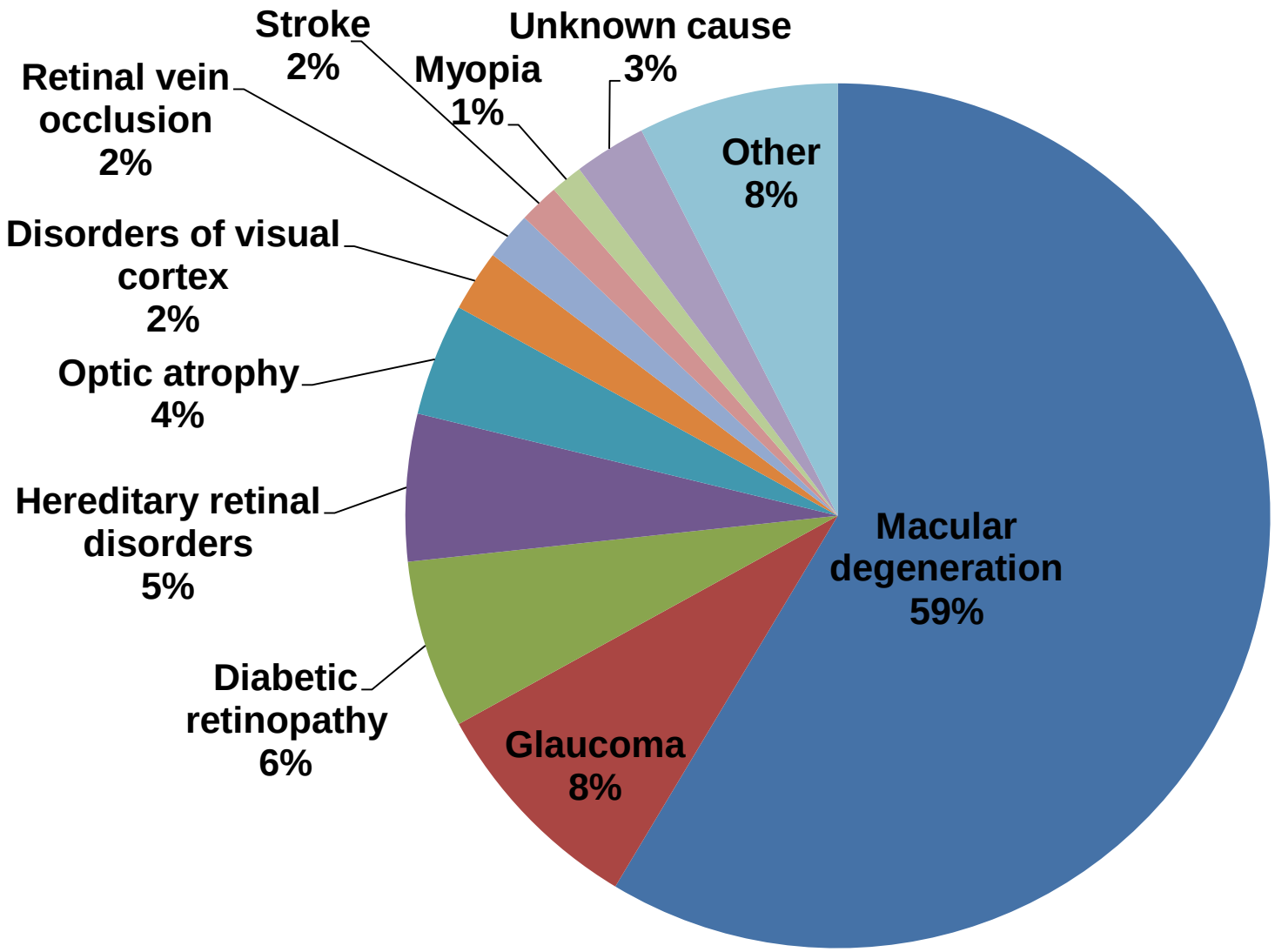
2006: Lucentis considered a miracle drug because it produced an average gain in vision; drugs in this class have sales over $5B/year



Rosenfeld et al., N Engl J Med 355:1419-1431, 2006

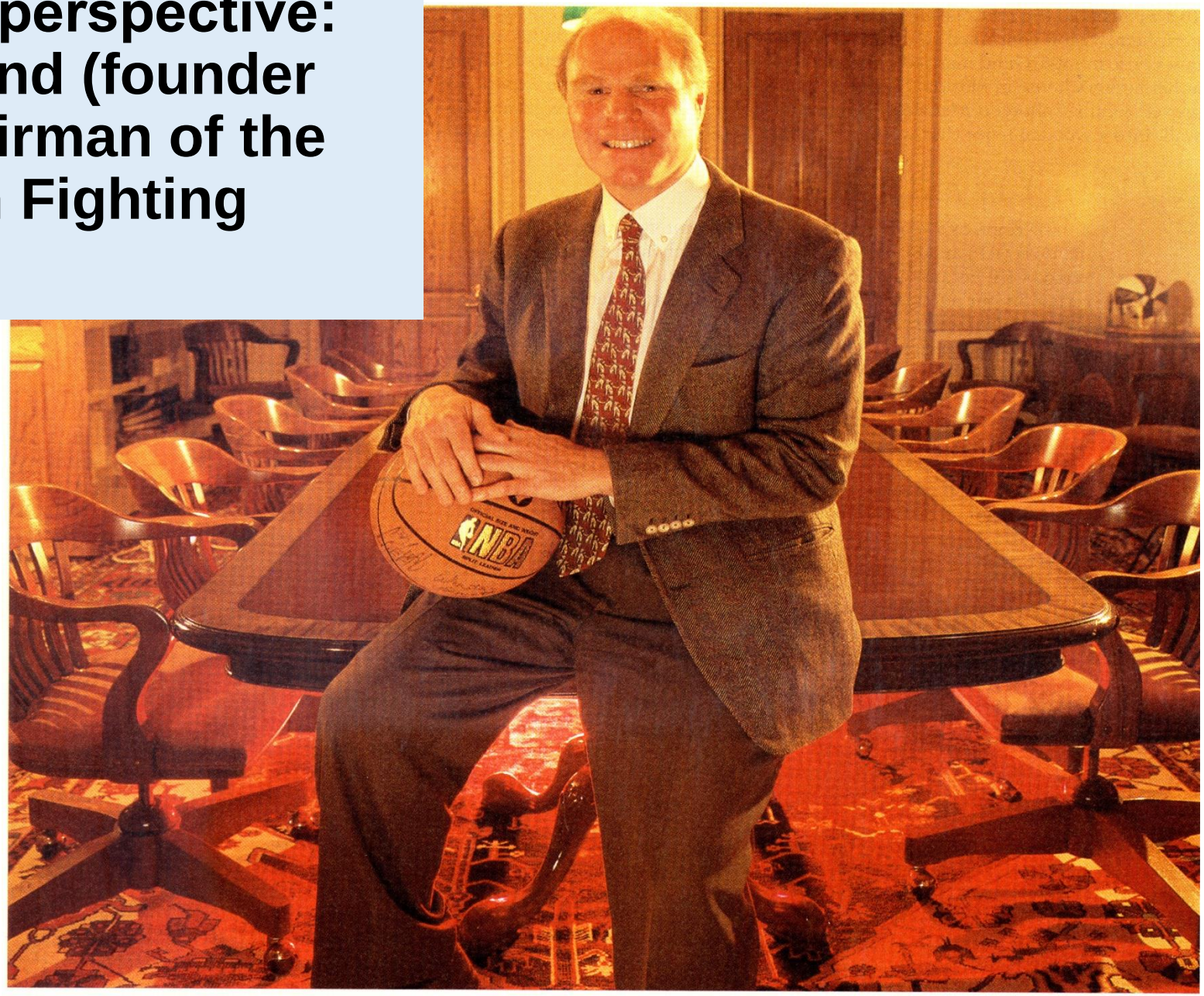
Despite the dramatic mean improvement, 60% of ranibizumab-treated eyes end with vision less than 20/40

Key need in ophthalmology: prevent blindness



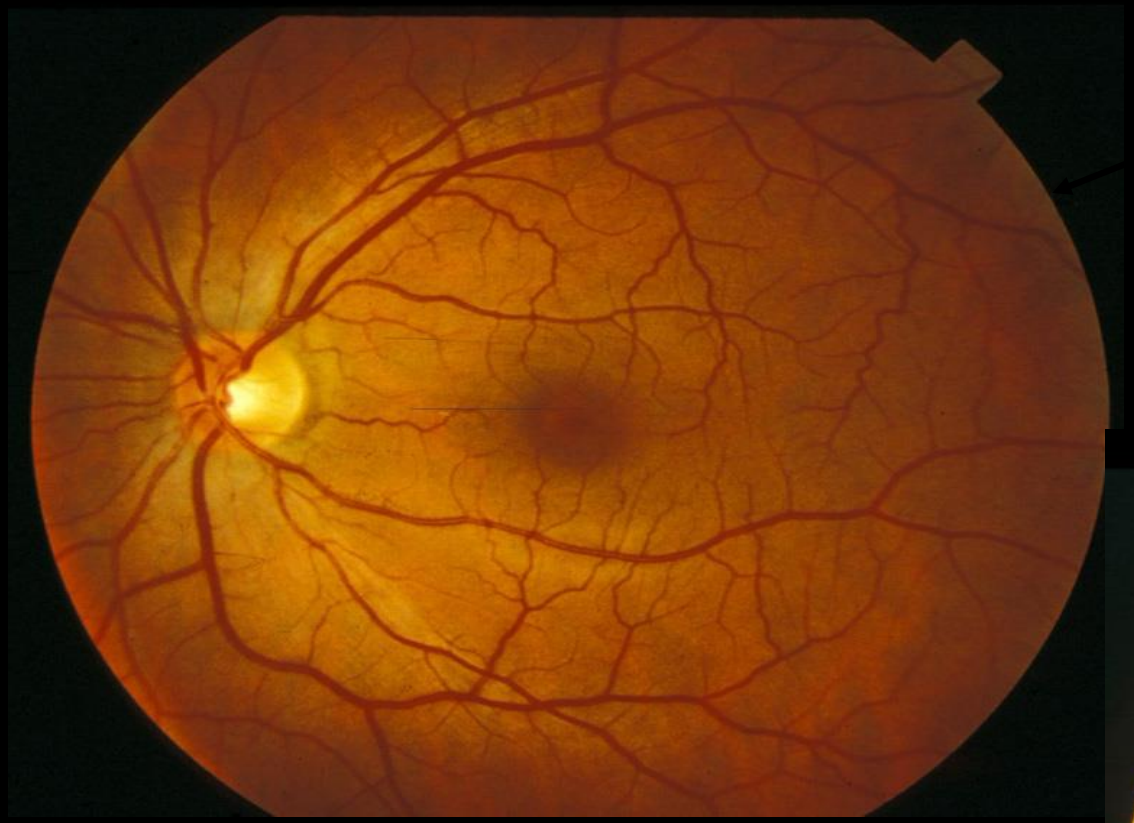
Bunce C et al. Causes of blind and partial sight certifications in England and Wales. Eye 24:1692-1699, 2010

A patient's perspective: Gordon Gund (founder and co-chairman of the Foundation Fighting Blindness)

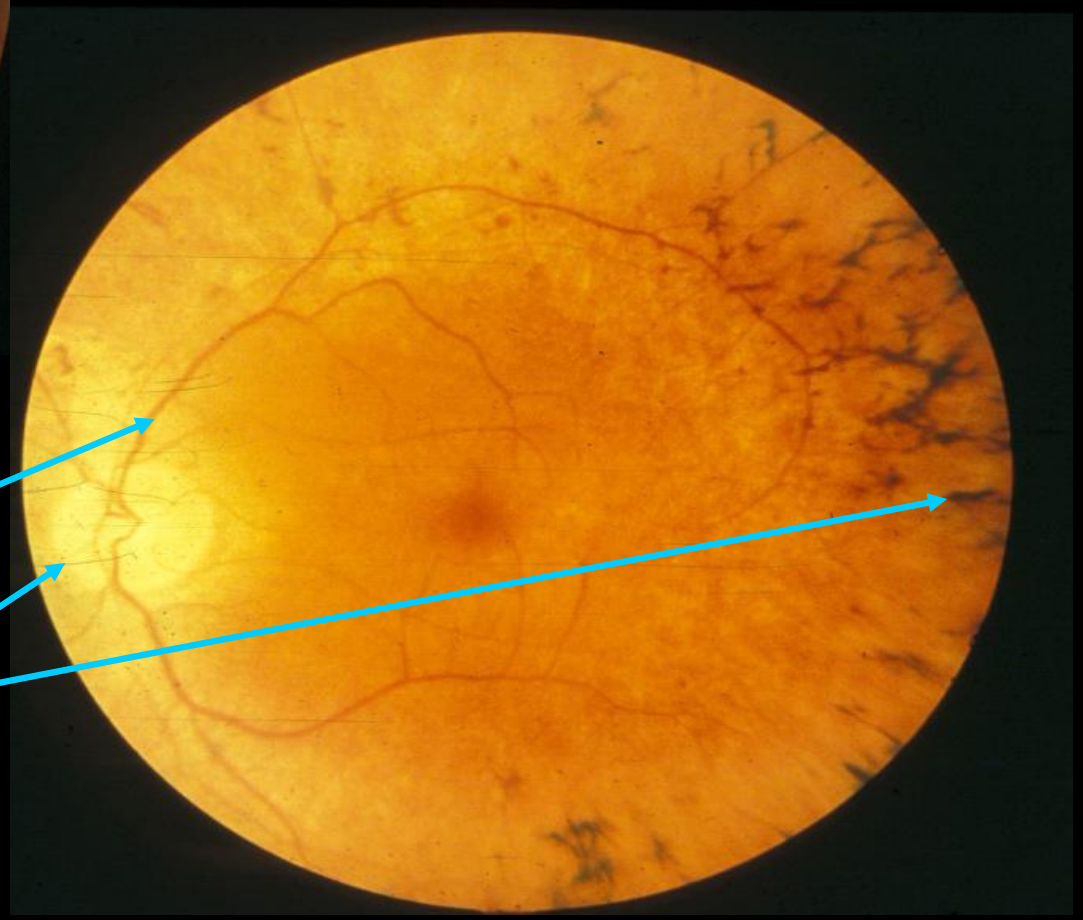


Gund in the conference room of his company in Princeton, New Jersey. He holds an NBA basketball signed by members of his team, the Cleveland Cavaliers.


Coca-Cola

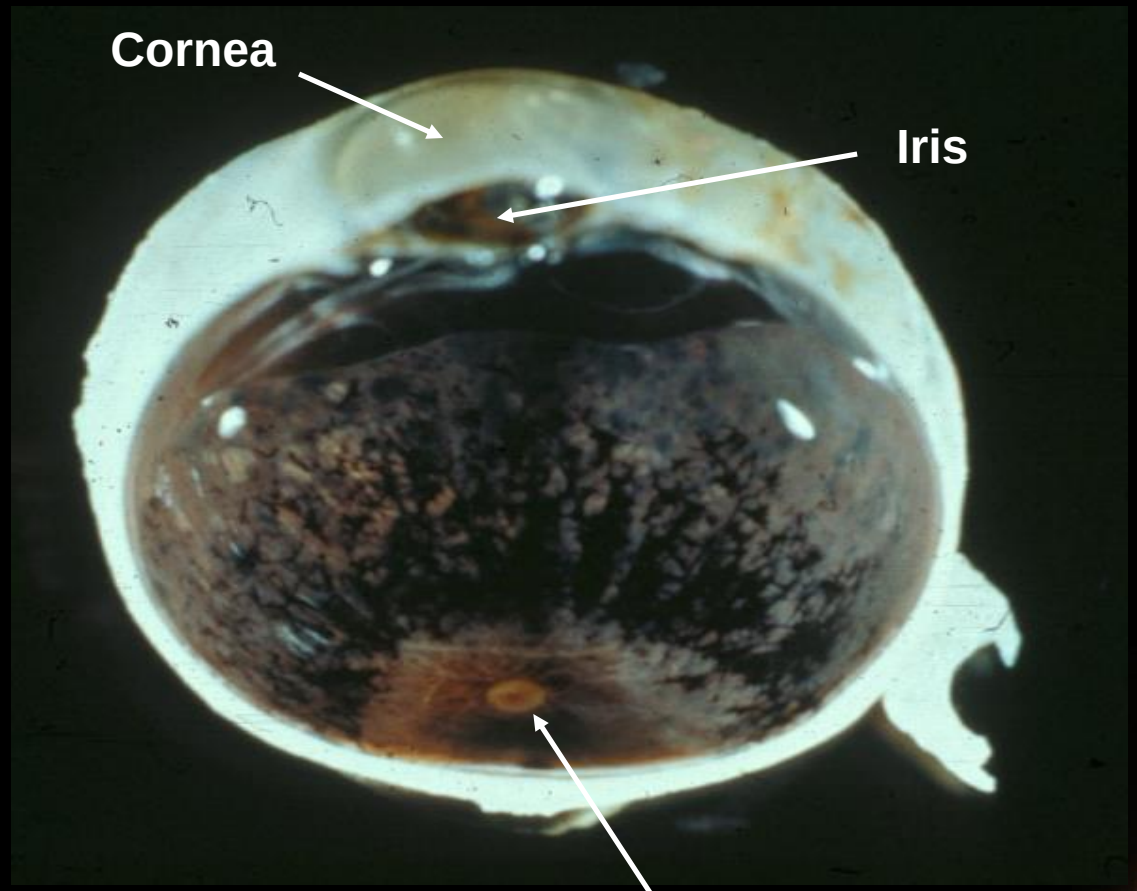


Normal human fundus (left eye)

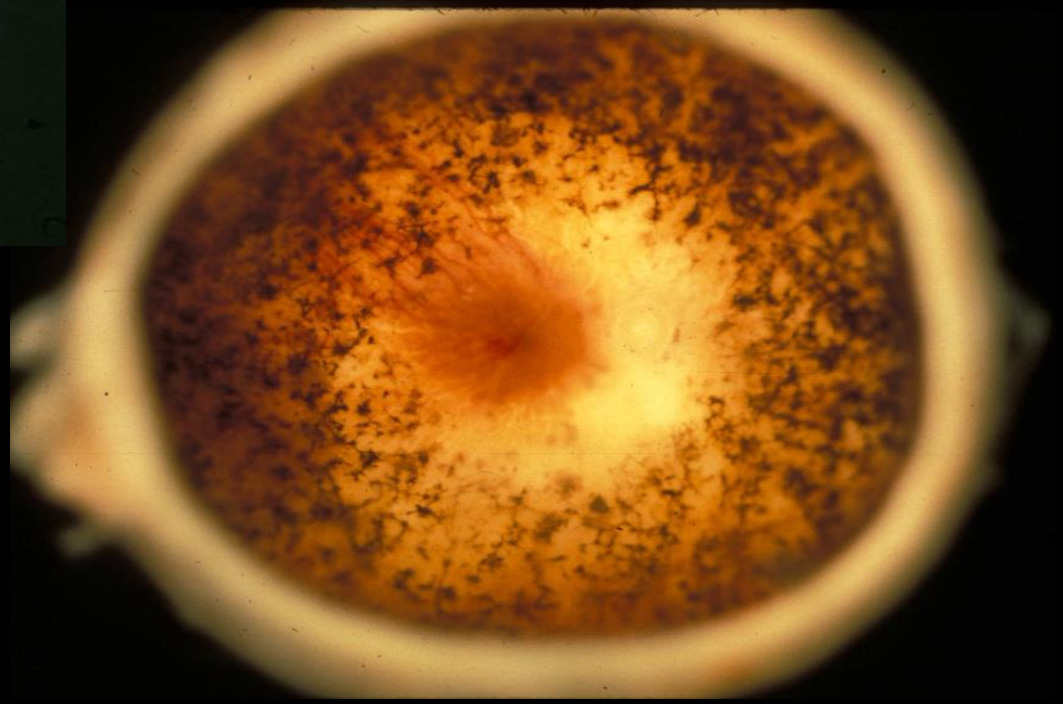


Fundus of patient with
retinitis pigmentosa (left eye)

1. Attenuated blood vessels
2. Bone-spicule-shaped intraretinal pigment deposits
3. Pale optic nerve head



Gross dissection of eyes from patients with retinitis pigmentosa obtained at autopsy



Normal retina

Nerve fiber layer

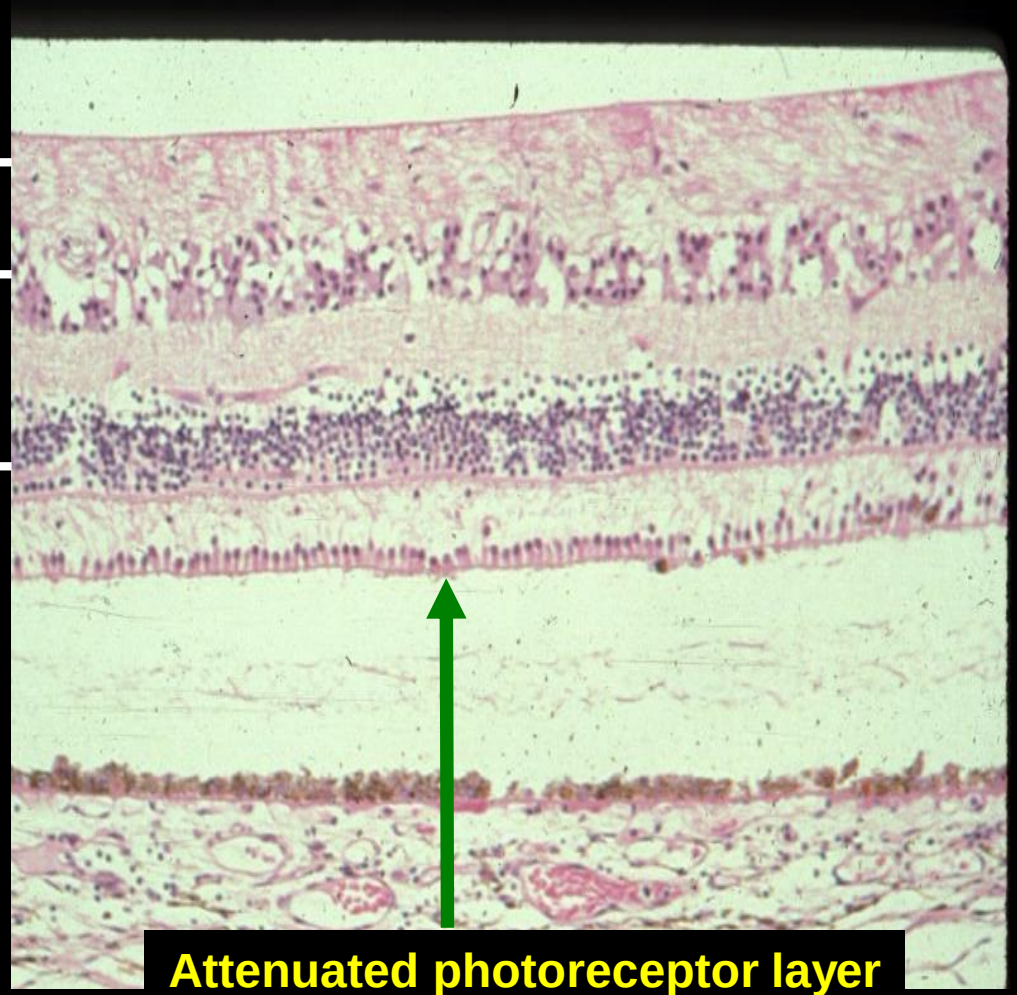
Ganglion cells

Bipolar, horizontal amacrine, etc.

Rod and cone photoreceptors

Retinal pigment epithelium

Retinitis pigmentosa



Attenuated photoreceptor layer

Normal retina from:
https://library.med.utah.edu/WebPath/HISTHTML/NORMAL/NORM013.html

Normal retina

Nerve fiber layer

Ganglion cells

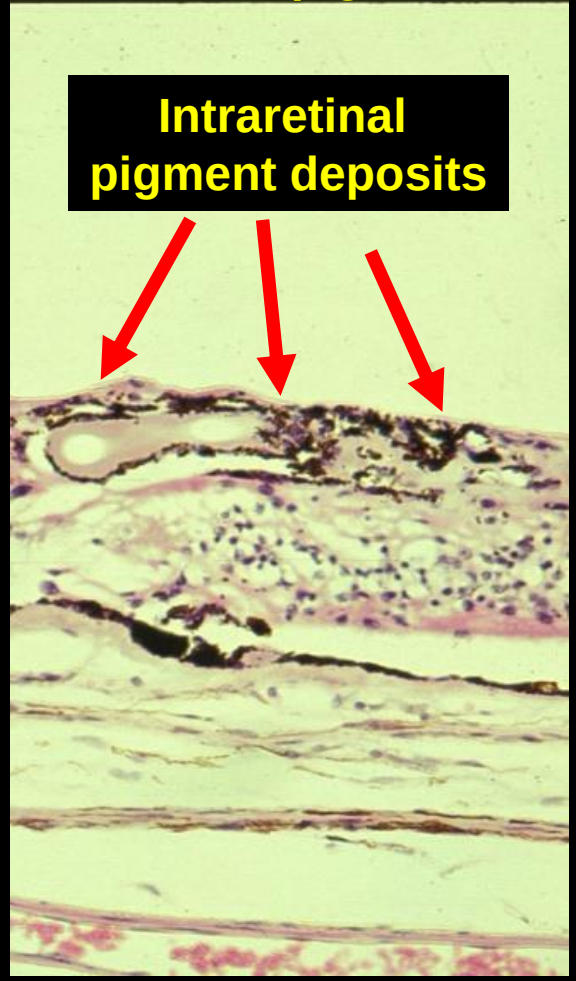
Bipolar, horizontal amacrine, etc.

Rod and cone photoreceptors

Retinal pigment epithelium

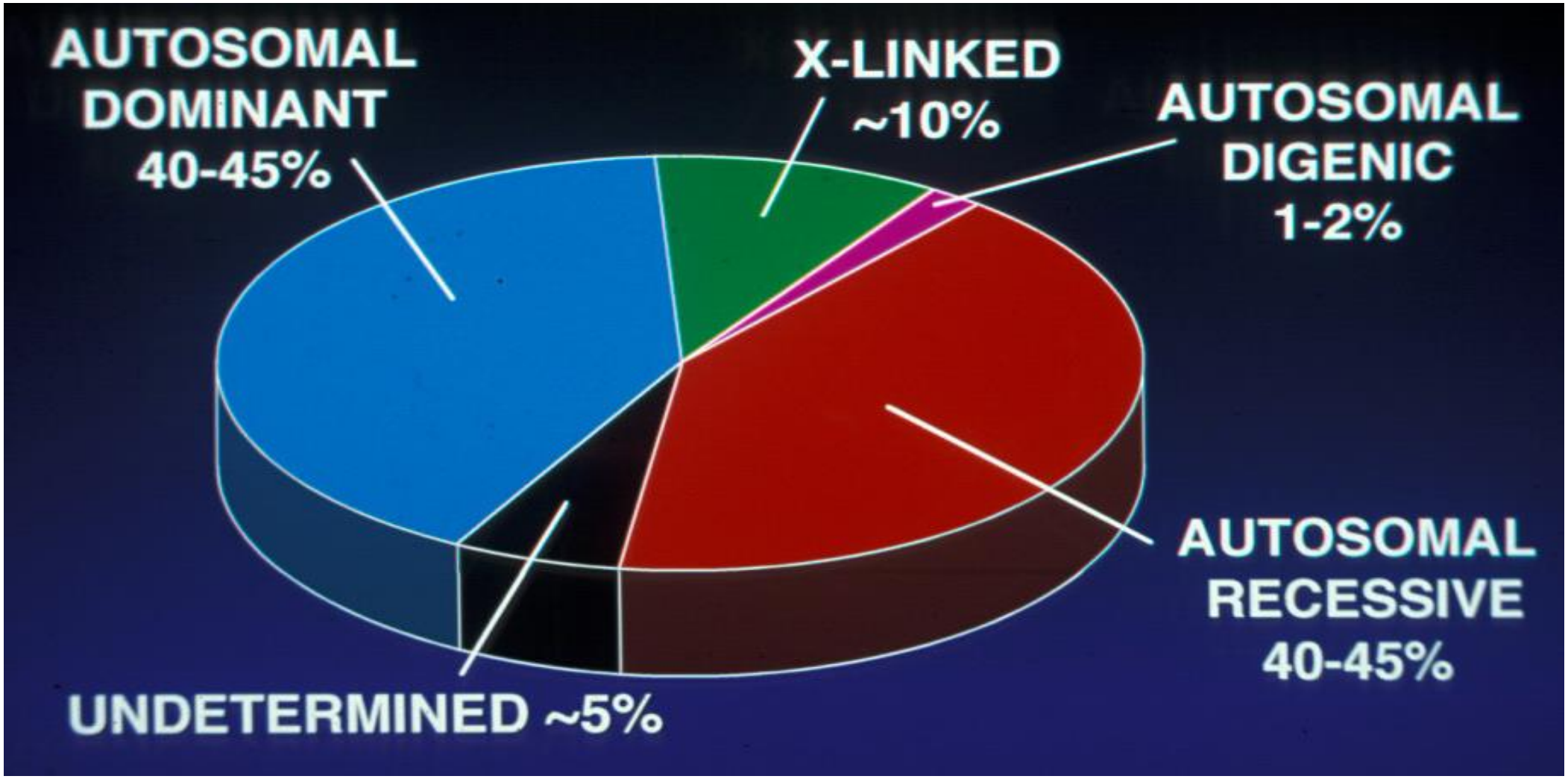
No longer identifiable

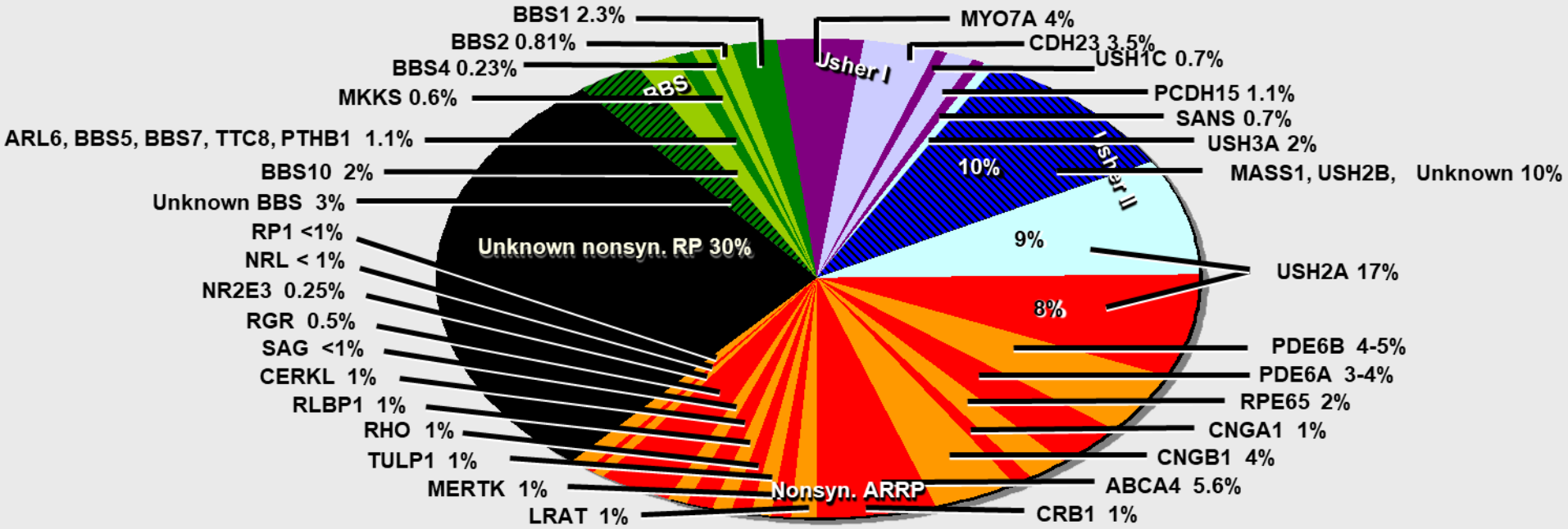
Region of severe degeneration in retinitis pigmentosa



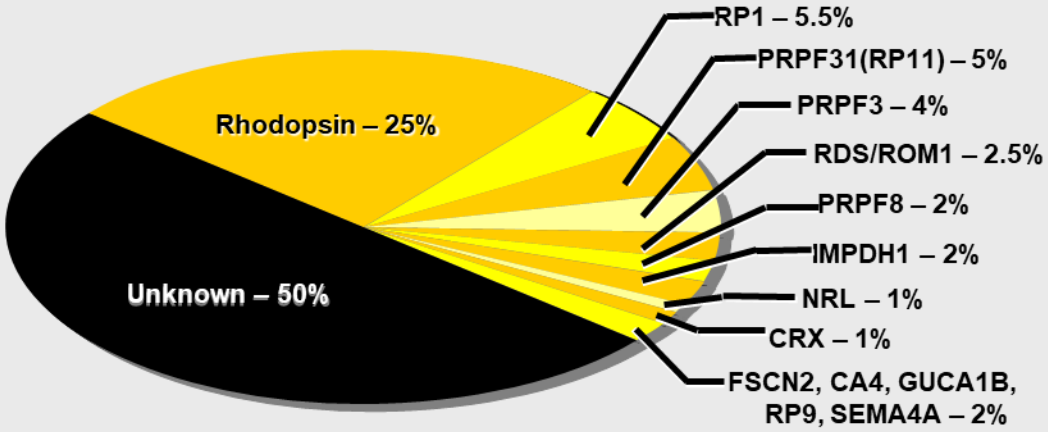
Normal retina from:
https://library.med.utah.edu/WebPath/HISTHTML/NORMAL/NORM013.html

Inheritance patterns in retinitis pigmentosa (including Usher syndrome and Bardet-Biedl syndrome)

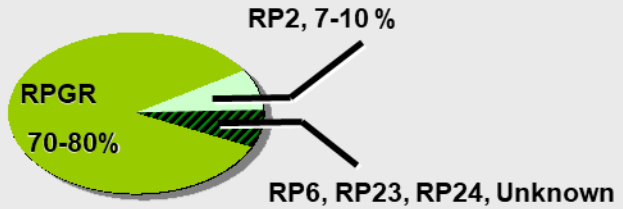




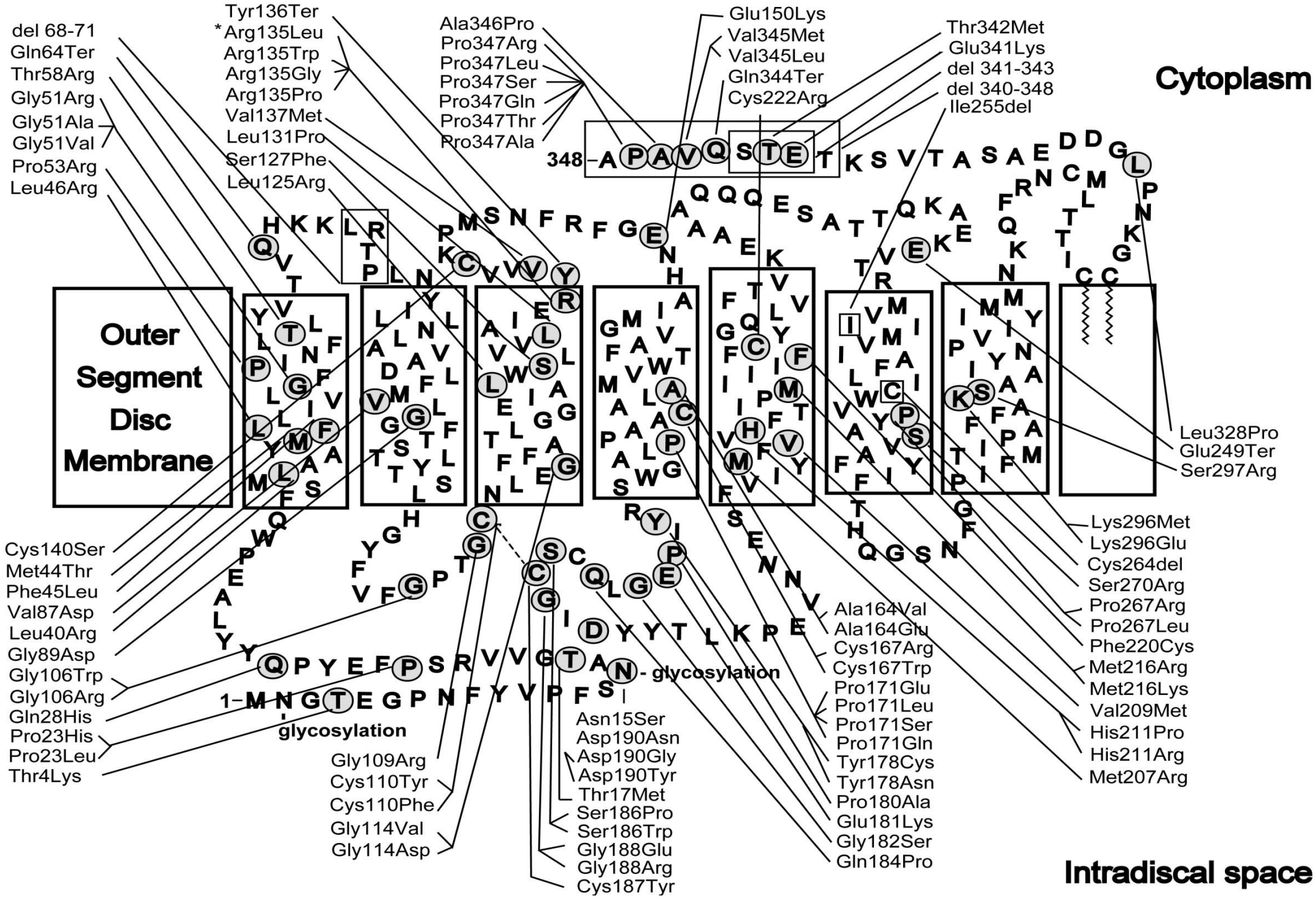
Autosomal recessive retinitis pigmentosa, 50 - 60% of cases



Autosomal dominant retinitis pigmentosa, 30 - 40% of cases



X-linked retinitis pigmentosa, 5 - 15% of cases


Cytoplasm
Outer Segment Disc Membrane
Intradiscal space
del 68-71
Gln64Ter
Thr58Arg
Gly51Arg
Gly51Ala
Gly51Val
Pro53Arg
Leu46Arg
Tyr136Ter
*Arg135Leu
Arg135Trp
Arg135Gly
Arg135Pro
Val137Met
Leu131Pro
Ser127Phe
Leu125Arg
Ala346Pro
Pro347Arg
Pro347Leu
Pro347Ser
Pro347Gln
Pro347Thr
Pro347Ala
Glu150Lys
Val345Met
Val345Leu
Gln344Ter
Cys222Arg
Thr342Met
Glu341Lys
del 341-343
del 340-348
Ile255del
348-APAVQSTE
Leu328Pro
Glu249Ter
Ser297Arg
Lys296Met
Lys296Glu
Cys264del
Ser270Arg
Pro267Arg
Pro267Leu
Phe220Cys
Met216Arg
Met216Lys
Val209Met
His211Pro
His211Arg
Met207Arg
Cys140Ser
Met44Thr
Phe45Leu
Val87Asp
Leu40Arg
Gly89Asp
Gly106Trp
Gly106Arg
Gln28His
Pro23His
Pro23Leu
Thr4Lys
1-MNGTEGPNFYVPFS
- glycosylation
- glycosylation
Gly109Arg
Cys110Tyr
Cys110Phe
Gly114Val
Gly114Asp
Asn15Ser
Asp190Asn
Asp190Gly
Asp190Tyr
Thr17Met
Ser186Pro
Ser186Trp
Gly188Glu
Gly188Arg
Cys187Tyr
Ala164Val
Ala164Glu
Cys167Arg
Cys167Trp
Pro171Glu
Pro171Leu
Pro171Ser
Pro171Gln
Tyr178Cys
Tyr178Asn
Pro180Ala
Glu181Lys
Gly182Ser
Gln184Pro

Most prevalent RP genes in the United States

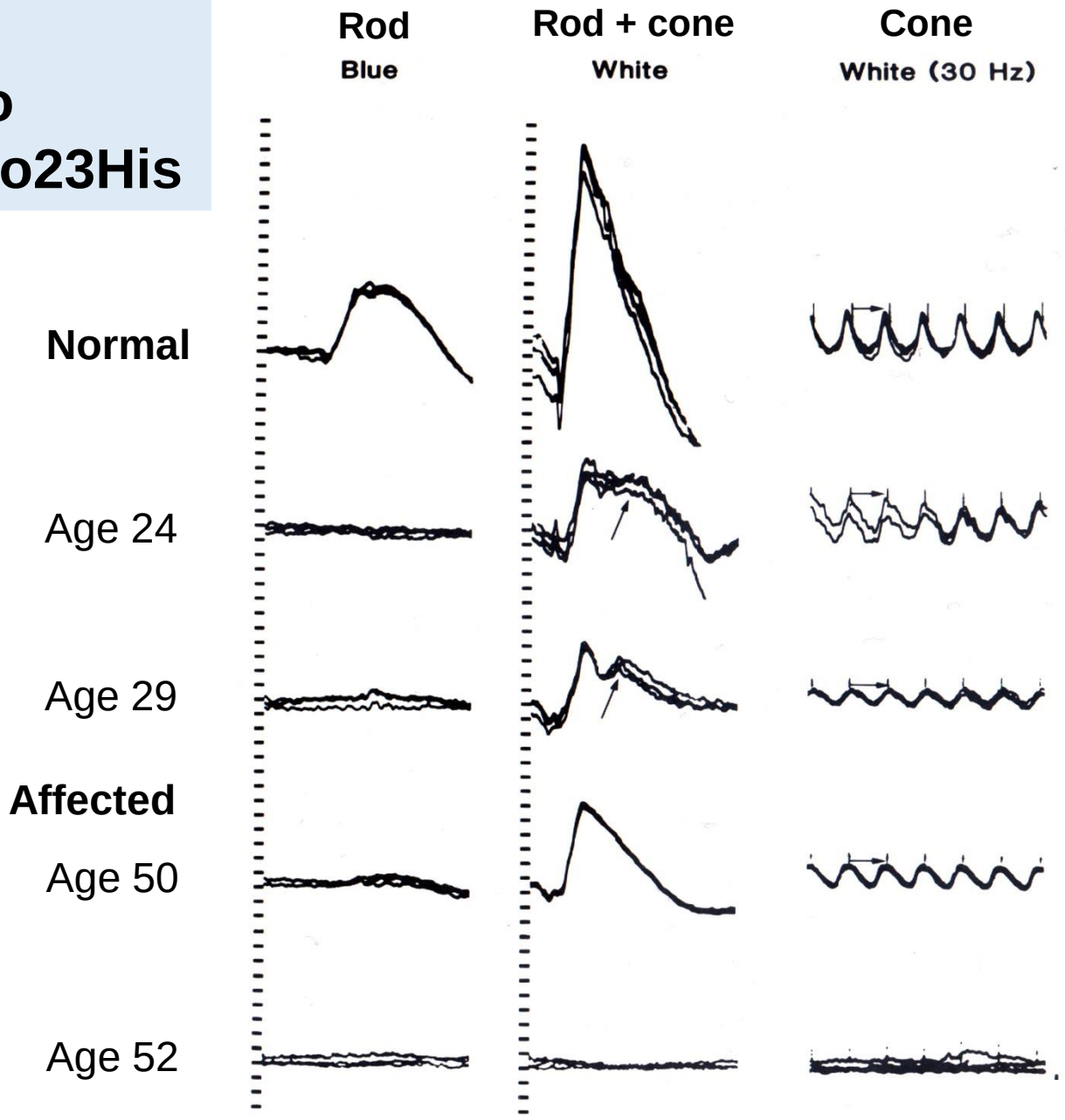
Rhodopsin: 25% of dominant RP;
10% of all RP

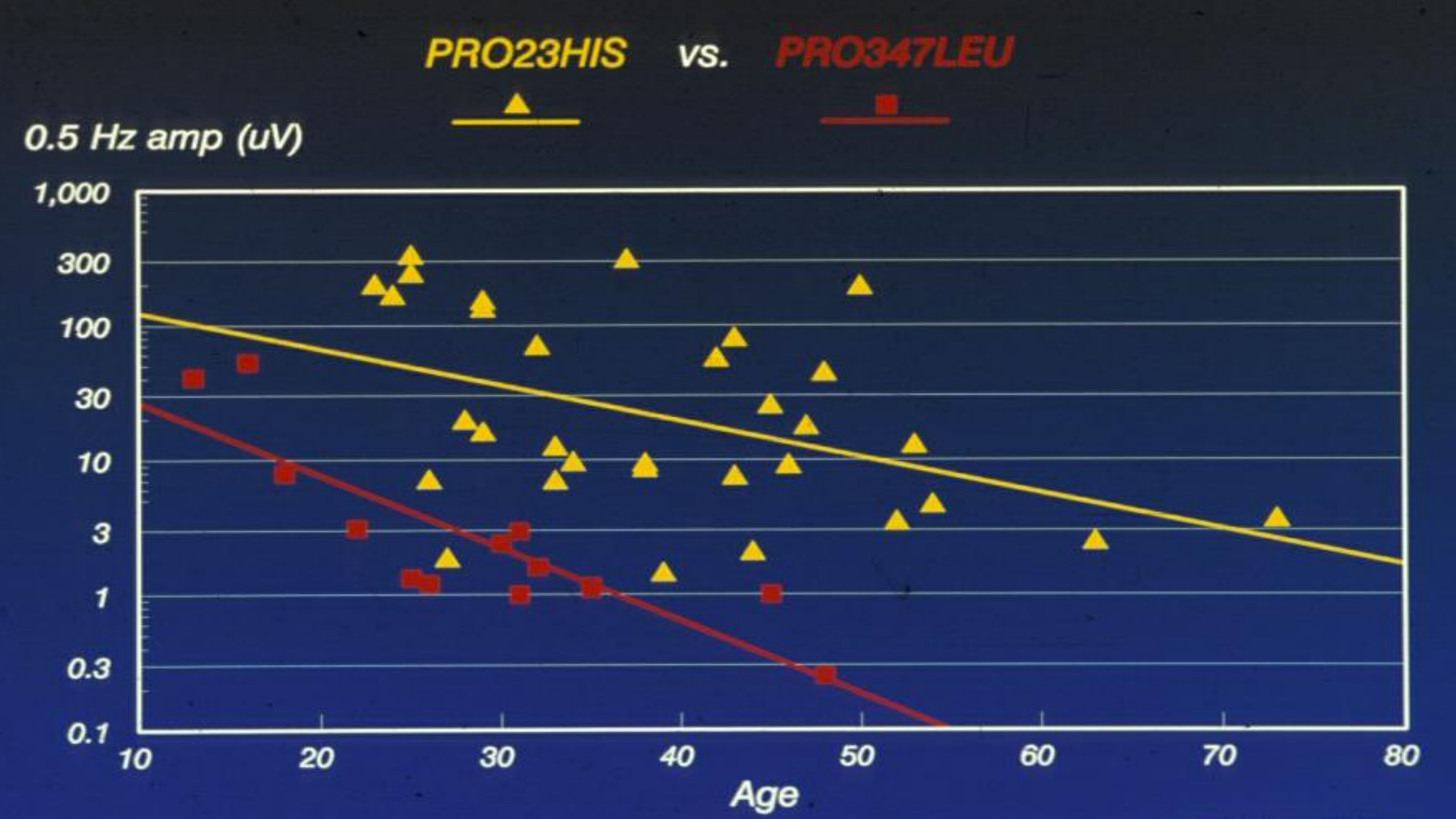
RPGR: 80-90% of X-linked RP;
8-9% of all RP

USH2A: >17% of recessive RP;
>8.5% of all RP

RHO + RPGR + USH2A = 27% of all RP

Electroretinograms (ERGs) in patients with dominant retinitis pigmentosa due to the rhodopsin mutation Pro23His




PRO23HIS vs. PRO347LEU
0.5 Hz amp (uV)
1,000
300
100
30
10
3
1
0.3
0.1
10
20
30
40
50
60
70
80
Age

Diverse development focus for retinitis pigmentosa: (a “focus” or a “shotgun approach”?) Review of clinicaltrials.gov (January, 2019)

Low molecular weight
L-dopa
inhaled oxygen
valproic acid
N-acetylcysteine
brimonidine
9-cis b-carotene

Biologics
QR-421A, QR-110
(ProQR-Ush2A)
CNTF
rhNGF

Dietary
Goji berries
Cannabis

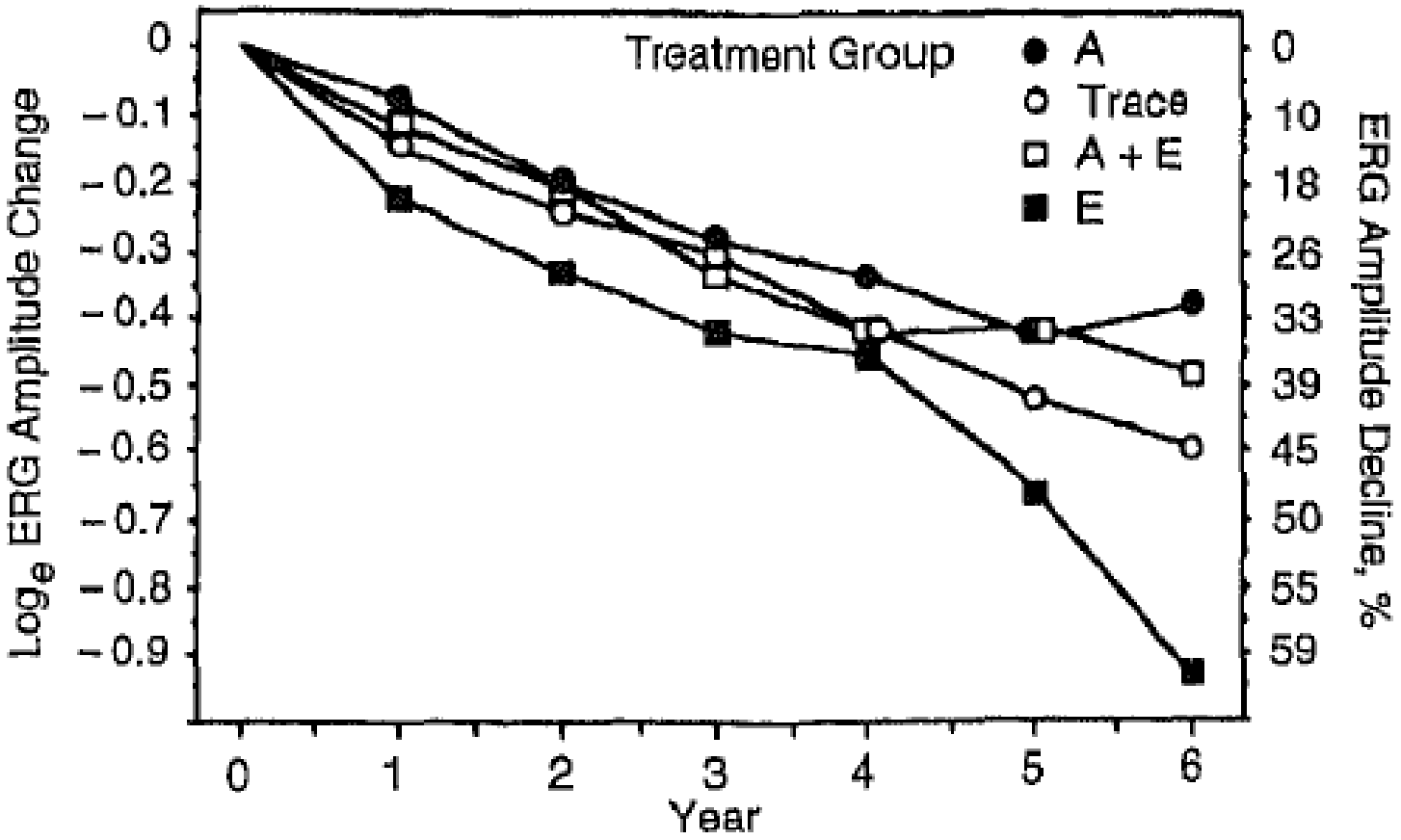
Alternative medicine
Acupuncture
Electro-acupuncture
Exercise

Electronic
Retinal implants
Transcorneal stimulation

Gene therapy
RLBP1
PDE6B
RPGR
RPE65
REP1
Myo7A
Optogenetic payload

Cell therapy
Bone marrow-mesenchymal cells given intravitreally or subretinally
Retinal progenitor cells

Vitamin A supplement for retinitis pigmentosa: possible benefit based on a single "phase III" trial



~ 160 patients/arm enrolled;

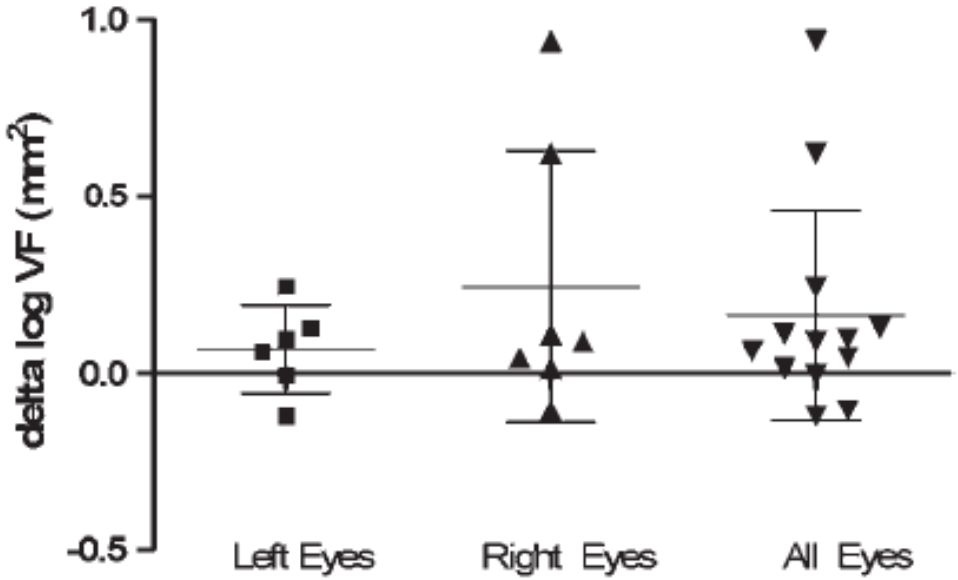
However, only ~ 60 patients/arm followed through years 5-6.

Berson EL et al., Arch. Ophthalmol. 111:761-772, 1993

Valproic acid for retinitis pigmentosa: anecdotal benefit in 2011 followed by disappointing consequences

2011:

Change in visual field
Oral valproic acid x 3 months



Clemson CM et al., Br. J. Ophthalmol. 95:89-93, 2011

2012:

Oral valproic acid x 4 months

Age (years)	Eye	Baseline Snellen BCVA	Final Snellen BCVA
8.2	OD	20/70	LP
	OS	20/80	HM
15.6	OD	20/160	20/300
	OS	20/200	20/600
34.6	OD	20/300	20/400
	OS	CF 5′	CF 4′

Sisk RA, Br. J. Ophthalmol. 95:89-93, 2012

2018: **90 patients, 50:50 randomization, 12 months of therapy: “small but statistically significantly worse outcome for the valproic acid group”**

Birch DG et al., JAMA Ophthalmol. 136:849-856, 2018

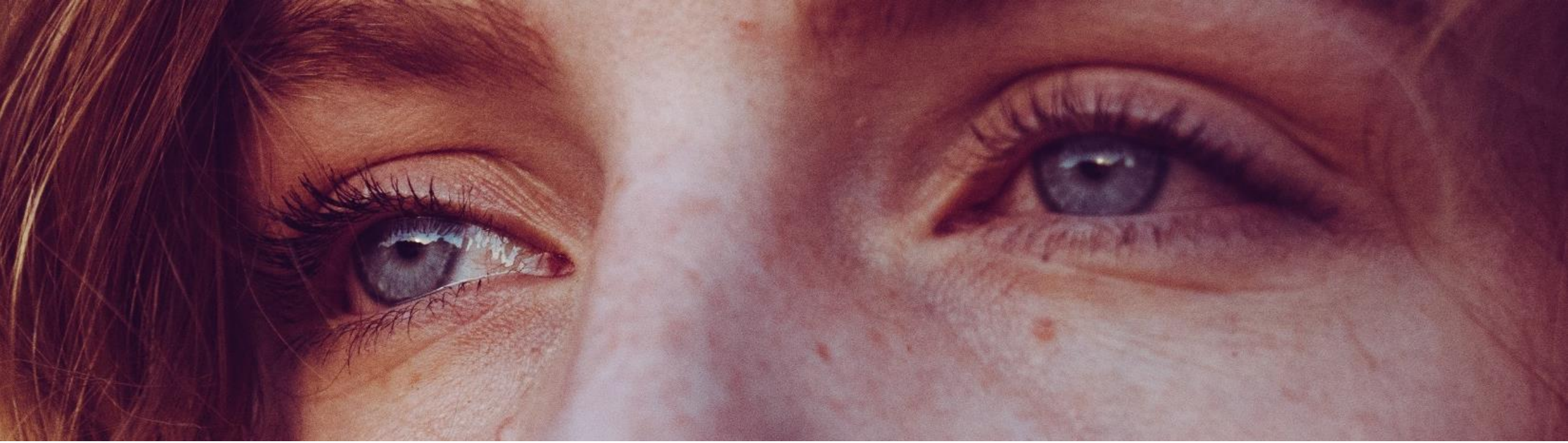
How the ProQR therapies are addressing unmet need in inherited retinal blindness

Vanguard program:

- **QR-110 for Cys998X mutation in CEP290 (congenital retinal blindness)**

Successor programs in two of the most prevalent forms of retinitis pigmentosa:

- **QR-421 for mutations in exon 13 of USH2A (Usher syndrome 2A)**
- **QR-411 for c.7595-2144A>G mutation in USH2A (Usher syndrome 2A)**
- **QR-1123 for the Pro23His mutation in the rhodopsin gene (dominant RP)**
  - **Knock-down of mutant allele allowing normal allele to serve retina**
  - **(Heterozygotes for a rhodopsin null allele have vision throughout life)**

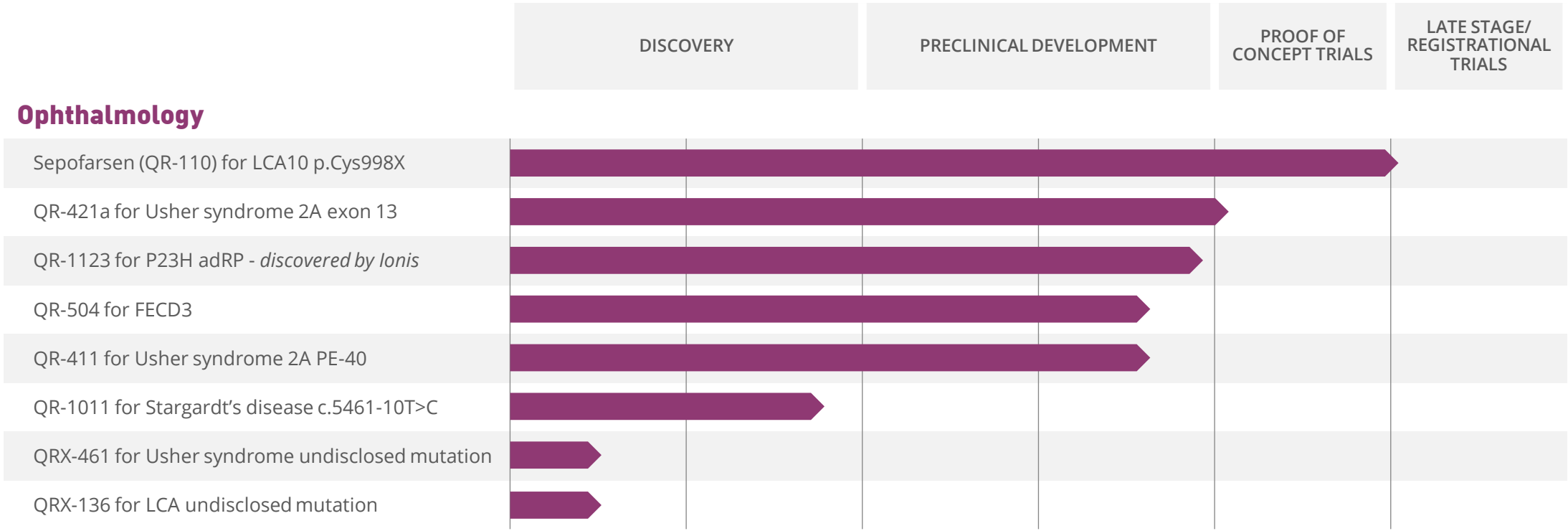


Creating Medicines

Early Development Pipeline

Peter Adamson, Ph.D., *Head of Ophthalmology Research*

ProQR Ophthalmology pipeline



QR-1123 for P23H adRP

Gapmer targeting autosomal dominant RP due to the P23H mutation in RHO

P23H adRP

Progressive reduction in night & peripheral vision. Blindness is frequent in mid-adulthood

No therapy available

~2,500 patients with P23H adRP in United States

QR-1123

Goal: Restore vision/prevent vision loss in patients with P23H adRP

Locally administered in the eye. Routine intravitreal procedure

Anticipated infrequent dosing of 4 times a year or less

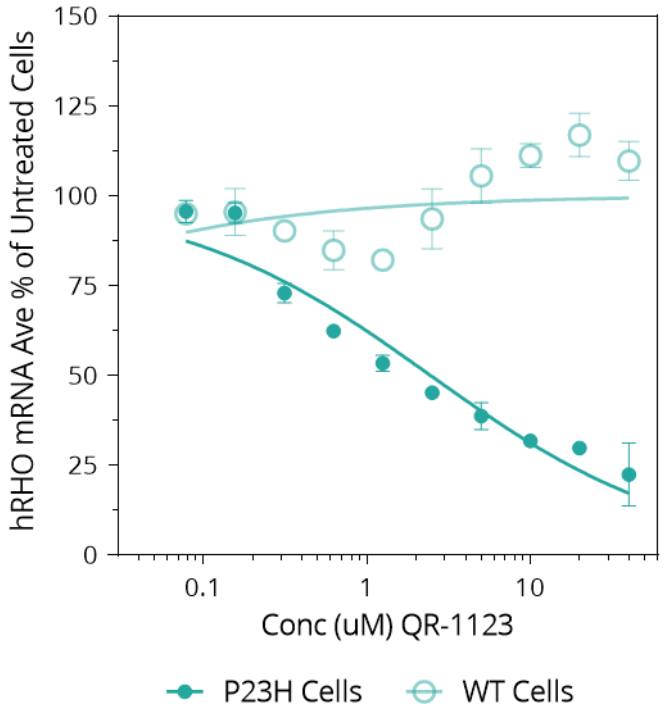
- ✓ Established modality in eye
- ✓ Strong preclinical proof of concept in vivo
- ✓ In-licensed from Ionis Pharmaceuticals
- ✓ Majority of IND enabling activities completed
- ✓ 2 year Natural History Study is completed and will be used to accelerate clinical development

Next steps

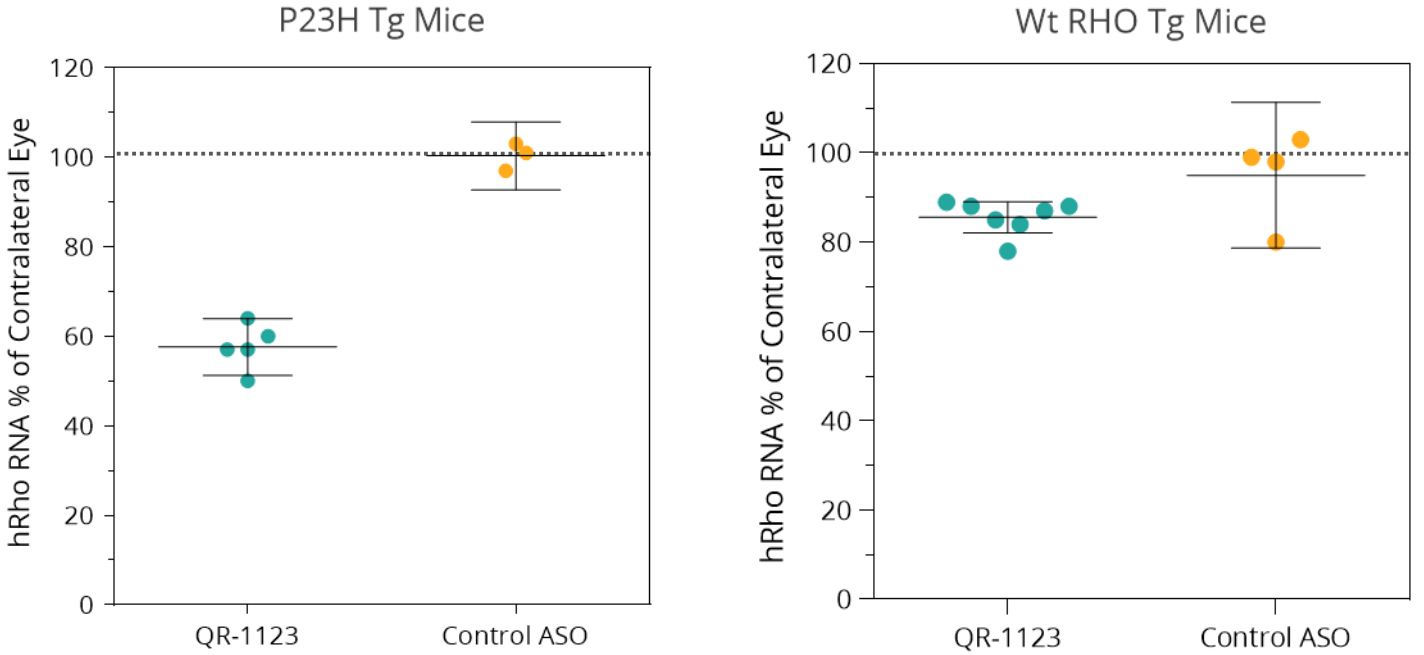
- Phase 1/2 trial expected to start in 2019
- Clinical development similar to QR-421a

QR-1123 is specific for P23H allele

Strong and specific suppression of P23H in cells



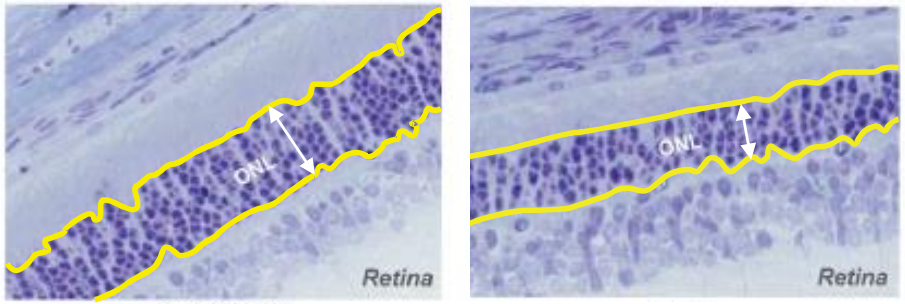
QR-1123 is selective for P23H *in vivo*



QR-1123 preserves ONL and improves ERG in P23H rat model

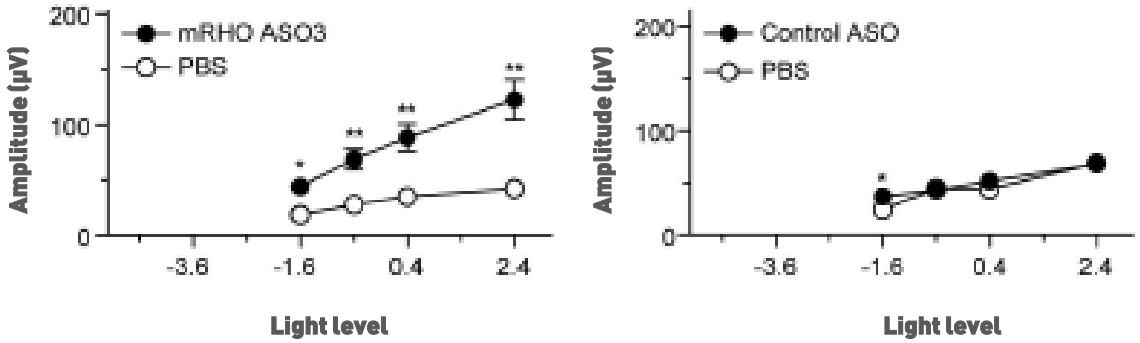
QR-1123 surrogate preserves ONL In P23H Tg rat

mRHO AS03 PBS



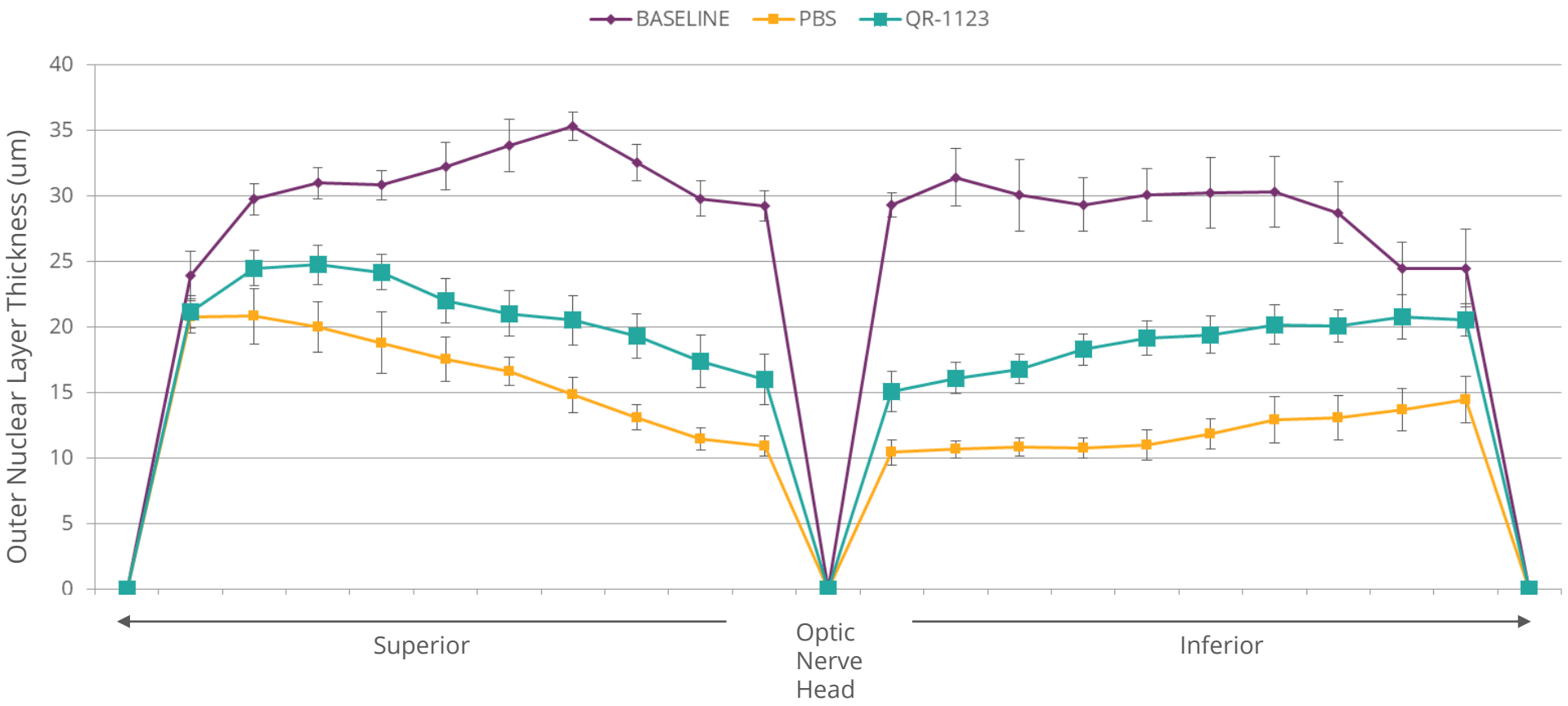
QR-1123 surrogate improves ERG in P23H Tg rat strong correlation with ONL preservation

QR-1123 surrogate Control oligo



Murray et al., 2015 IOVS 56: 6362

QR-1123 reduces retinal degeneration in humanized P23H mice



Overview: QR-1123 for P23H adRP

mRNA profile restoration

- Increase in rhodopsin mRNA profile and reduction in mutant mRNA
- Strong selectivity for mutant over WT mRNA

Local (intravitreal) delivery to the eye

- Eye well validated target for oligos
- Efficient delivery to photoreceptor layer in the retina

Evidence of improvement in photoreceptors

- Evidence of functional improvement (ERG) in knock-in Tg mice
- Evidence of histological protection in human P23H opsin KI mouse

Clinical candidate selected

- QR-1123 selected as clinical candidate

Development

QR-411 for Usher syndrome

Designed to treat genetic eye disease in Usher syndrome

Usher

Develop hearing loss and blindness in childhood and turn completely blind by mid adulthood

PE40 mutation affects **~1,000** patients in Western world

QR-411

For Usher **PE40** no therapy available

Strong PoC

Strong preclinical PoC in human organoid models. Development candidate selected

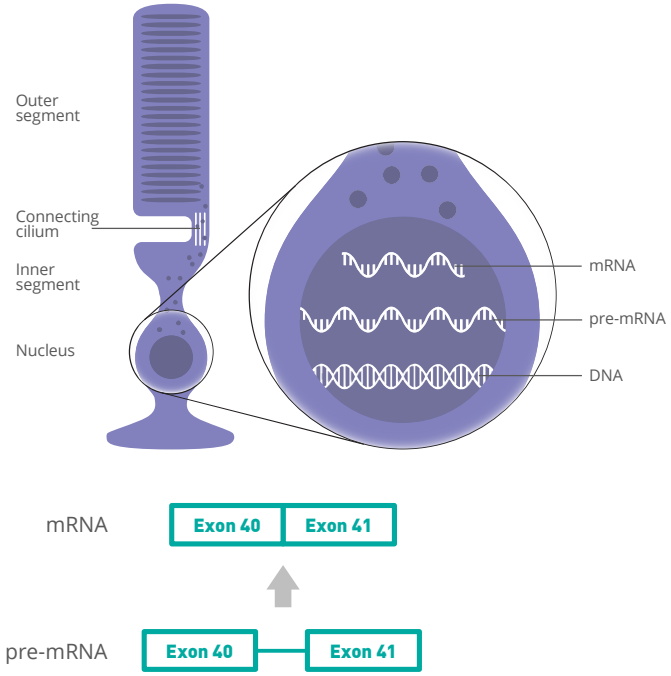
- ✓ RNA is established modality in eye
- ✓ Strong preclinical proof of concept in patient retinal organoids
- ✓ Orphan drug designation

Next steps

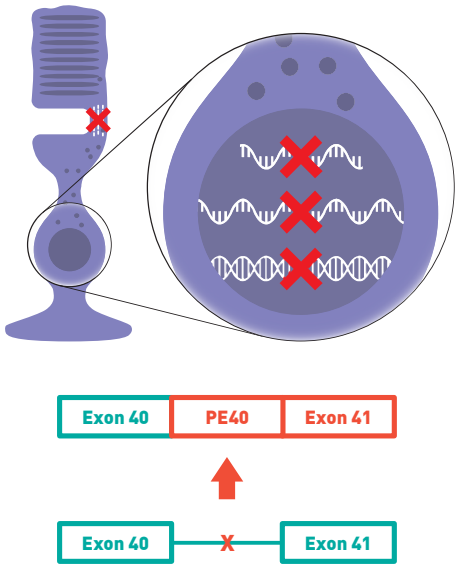
- IND-enabling studies expected to start in 2019
- Clinical development similar to QR-421a

QR-411 for RP in Usher syndrome

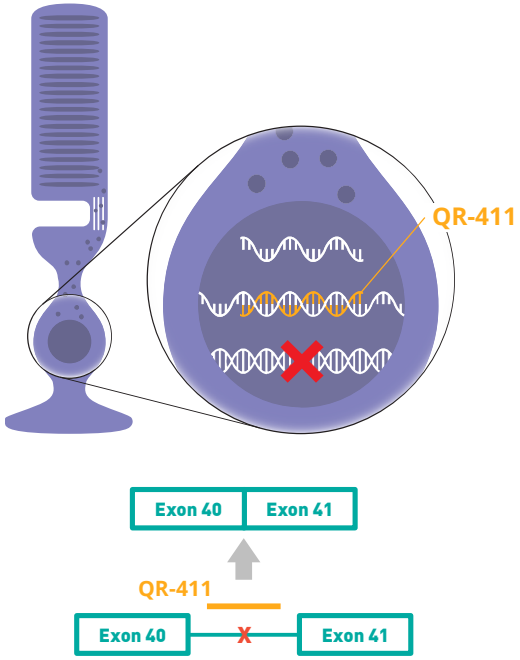
Splice correction for PE40 USH2A mRNA



In wild-type cells Usherin maintains photoreceptor structure and enables normal protein transport



In PE40 mutant cells protein transport is hampered and the outer segment degenerates

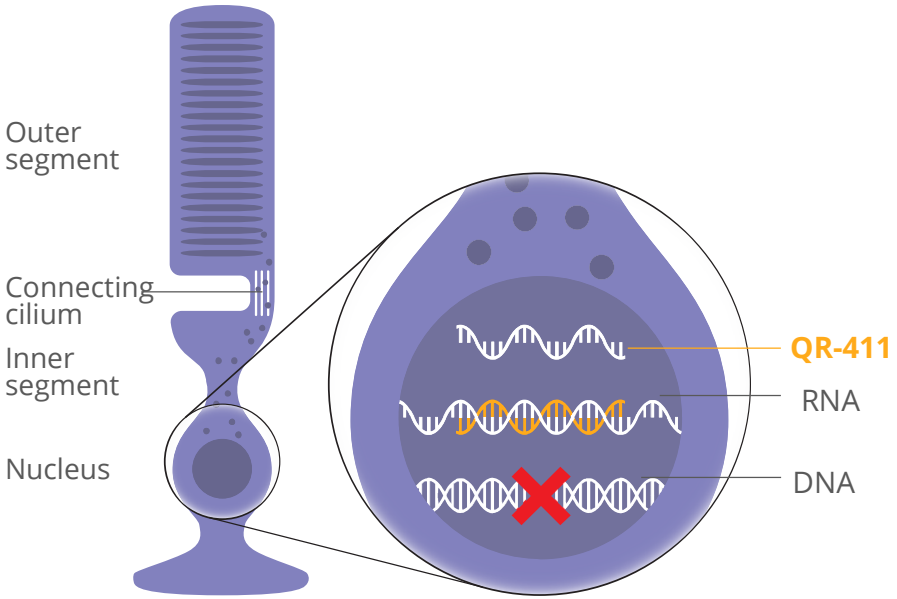


Exclusion of PE40 from the mRNA leads to wild-type Usherin protein

Identical molecular mechanism to sepofarsen - splice correction creating WT mRNA

QR-411 for Usher syndrome

USH2A PE40 splice correction



QR-411 - Clinical Development

- Design and endpoints very similar to that for QR-421a (RP) and QR-1123 (adRP)

QR-411 - Asset Characterization

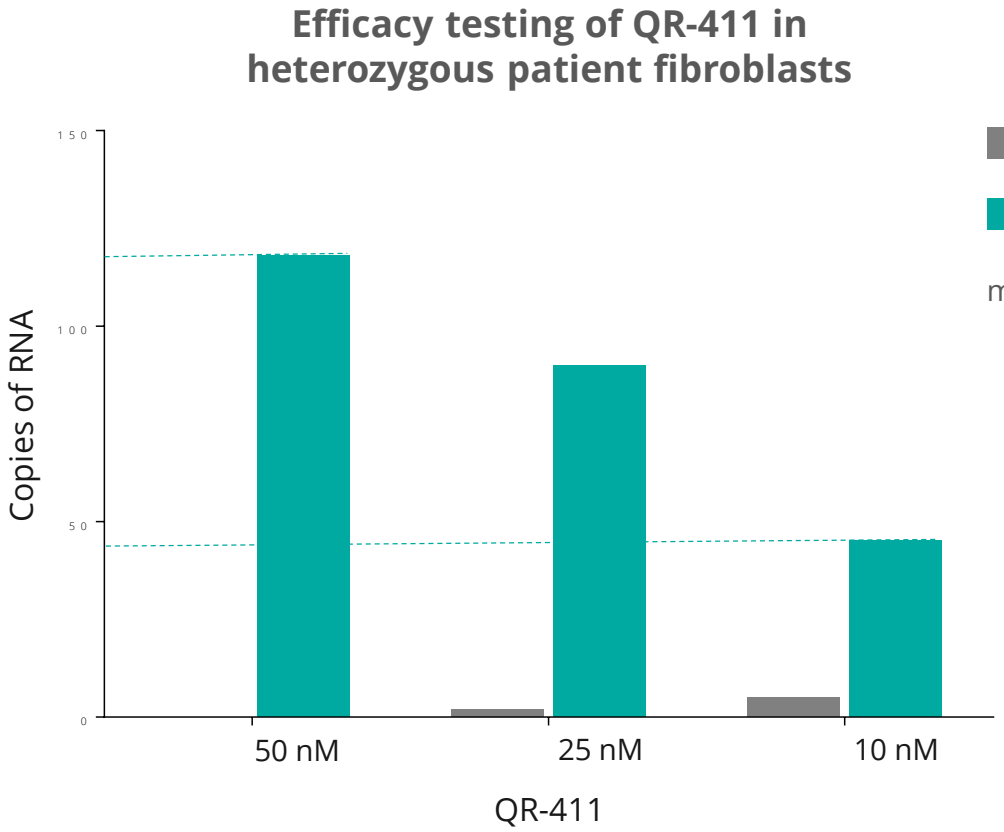
- Single stranded 20-mer RNA oligonucleotide
- Chemically modified for stability, safety, efficiency and uptake
- Well understood MoA
- Designed to target the USH2A PE40 mutation
- IVT administration, based on studies with LCA sepofarsen likely no detectable systemic exposure in animals

QR-411 - Data

- >95% effect in mediating Ush2A PE40 mRNA in patient derived fibroblasts and optic cups
- Ability to edit human Ush2A PE40 mRNA in human knock-in transgenic fish
- Ability to distribute to photoreceptor layer after IVT injection
- Initial tolerability studies in rabbits shows similar profile to sepofarsen

In vitro proof of concept

Dose-dependent effect of QR-411 on WT RNA in patient fibroblasts

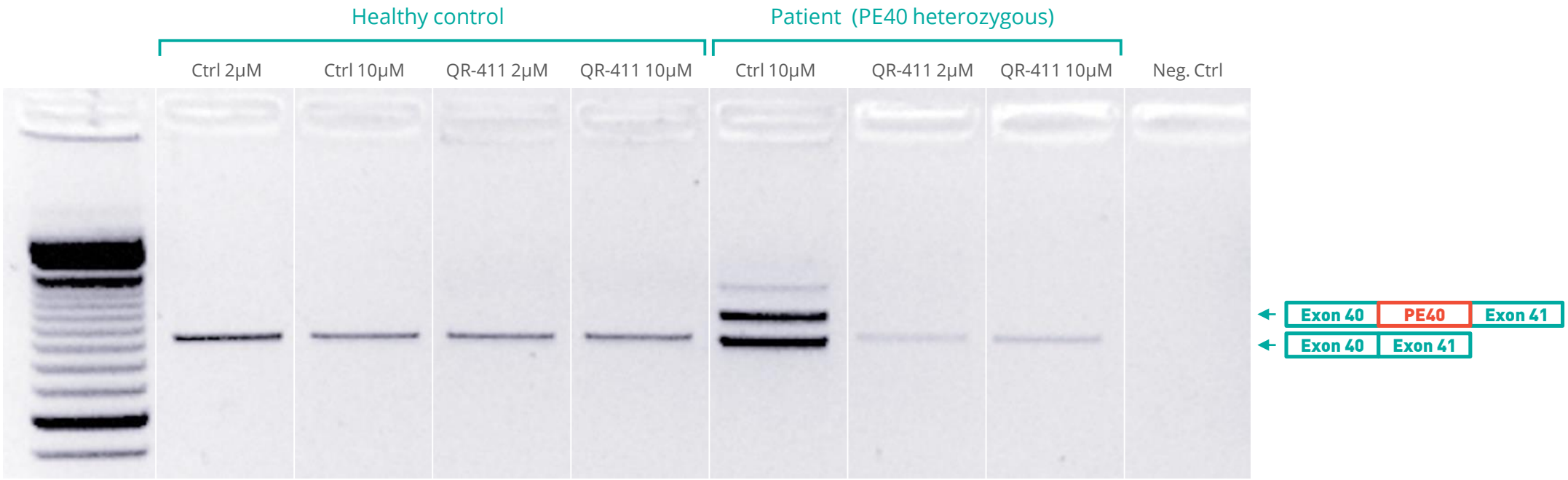


mRNA species undergoes NMD

- Sepofarsen showed similar responses in LCA patient fibroblasts
- Similar data for QR-411 in PE40 het retinal organoids at 2uM and 10uM concentrations (cf same efficacy range as sepofarsen approx. 100%)

In vitro proof of concept

QR-411 restores WT RNA in patient-derived iPSC optic cups



Erwin van Wijk, Radboudumc, Nijmegen, the Netherlands

Overview: QR-411 for USH2A PE40

mRNA profile restoration

mRNA profile restored to wild-type

Local (intravitreal) delivery to the eye

Eye well validated target for oligos

Efficient delivery to outer nuclear layer in the retina

mRNA profile restoration in optic-cups

mRNA profile shows PE40 skip in patient–derived optic cups retinal organoids

Clinical candidate selected

QR-411 selected as clinical candidate

Development

QR-1011 for Stargardt's disease

Stargardt's disease

Develop blindness in childhood and turn completely blind by mid adulthood

~7,000 patients with c.5461-10T>C in ABCA4 in Western world

QR-1011

For Stargardt's c.5461-10T>C in ABCA4 no therapy available

Strong PoC

Preclinical PoC and efficacy in human mini-gene models

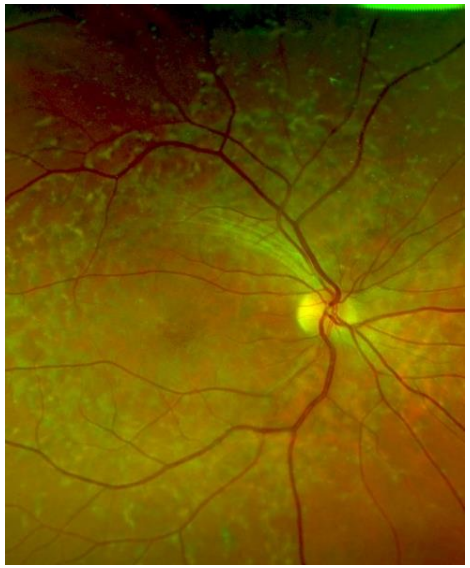
- ✓ RNA is established modality in eye
- ✓ Strong pre-clinical proof of concept

Next steps

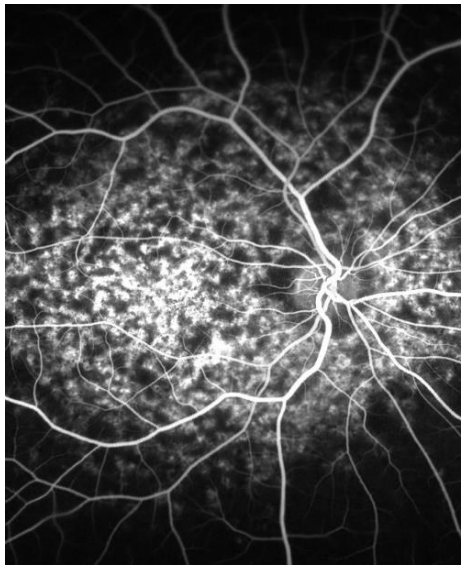
- Progression into retinal organoid

Stargardt's disease: clinical phenotype

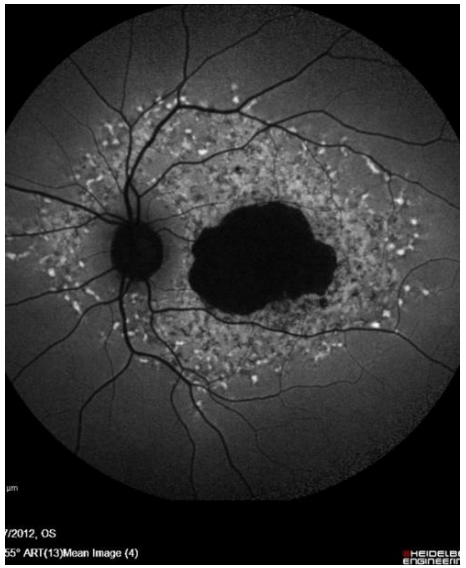
Color Fundus Photography (CFP)



Fluorescein Angiography (FA)



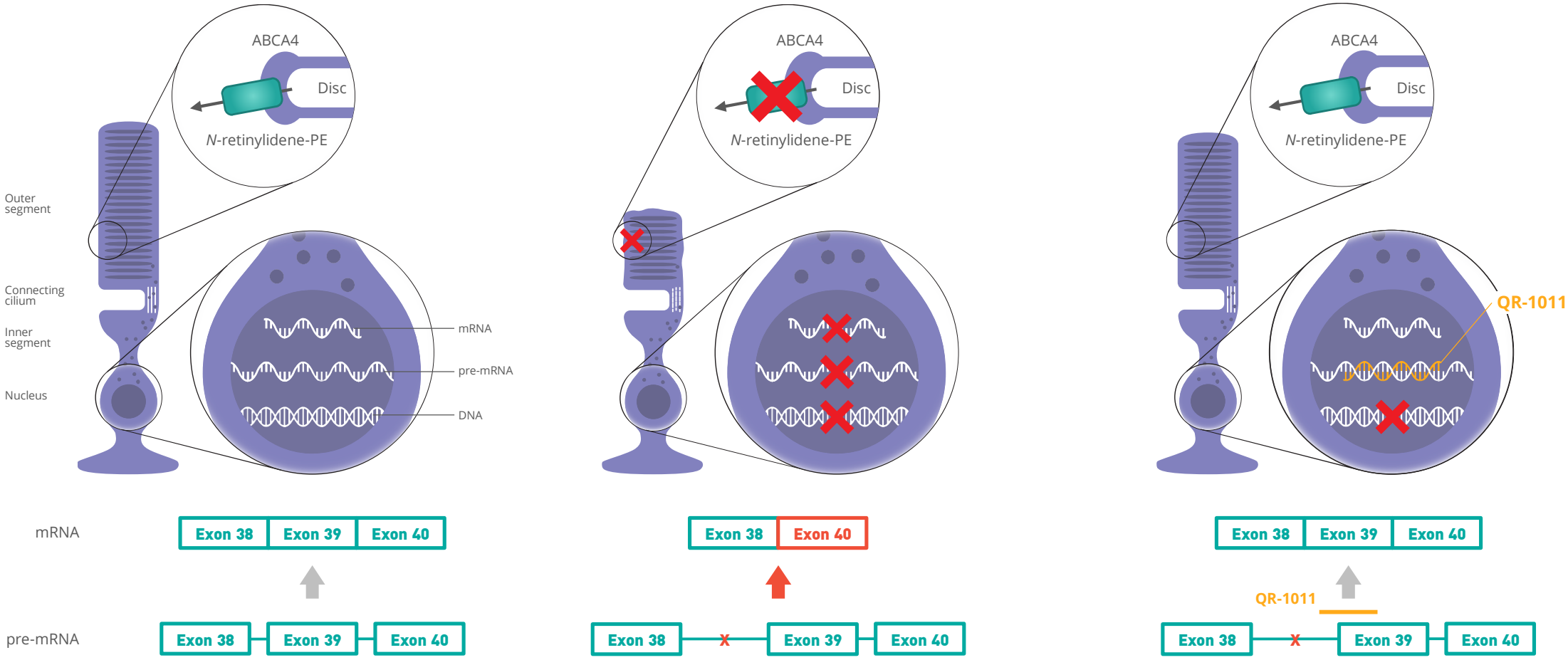
Fundus Autofluorecence (FAF)



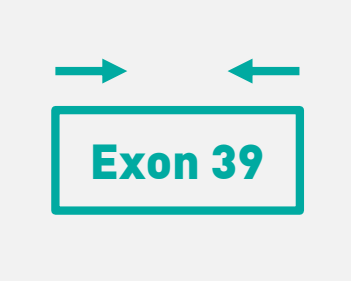
- Most frequent form of inherited juvenile macular degeneration
- Manifests as central vision loss and progresses to complete blindness
- Median onset of disease approx. 17 years
- Loss of RPE cells (scotoma)

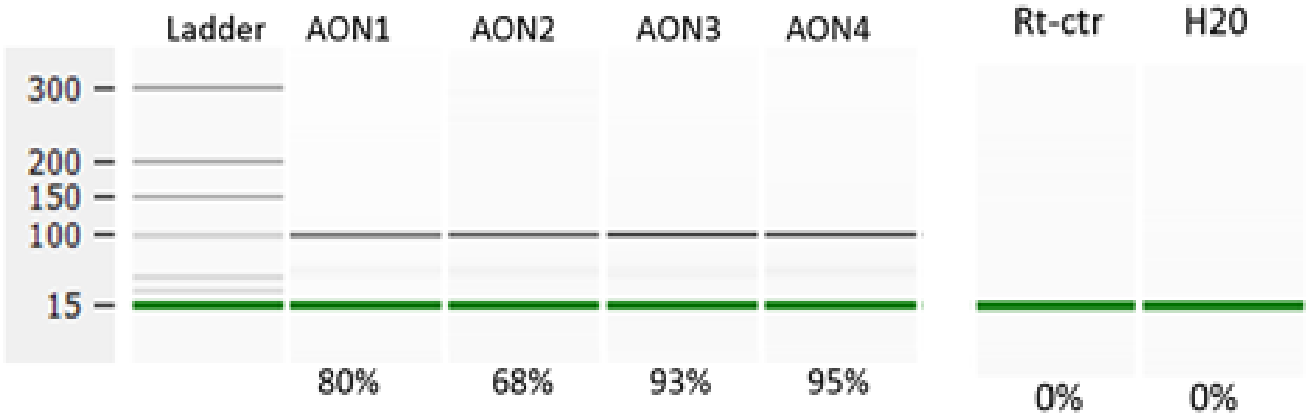
Prevention of Exon 39 exclusion

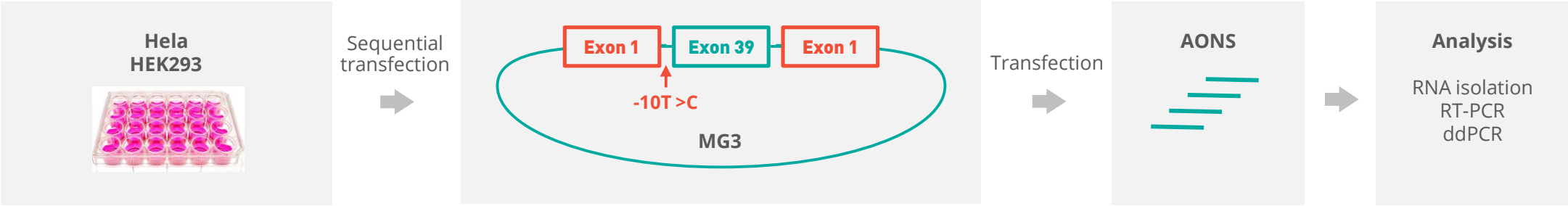
Splice correction



QR-1011 screening







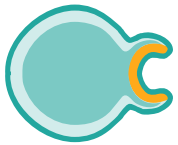
Next Steps is to optimize in human ABCA4 c5561-10C>T retinal organoids 'optic cups'

Ophthalmology: QR-1011 for Stargardt's disease

QR-1011 drives splice correction of mutant ABCA4 mRNA

Ex39 inclusion demonstrated in mutant ABCA4 mutant mini-gene construct upon treatment with a number of oligo sequences

QR-1011 profiling in retinal organoids



Ex39 exclusion to be confirmed in ABCA4 c5461-10T>C and restoration with QR-1011 in retinal organoids to be confirmed

Cells isolated from patient ABCA4 c.5461-10T>C

Renal epithelial cell already isolated from patient urine. Cells will begin re-programming into optic cups

QR-1011 chemistry optimization

Chemistry/sequence optimization ongoing

Local (intravitreal) delivery to the eye

Eye well validated target for oligos

Efficient delivery to photoreceptors (ONL)

Development

QR-504 for FECD3

Fuchs Endothelial Corneal Dystrophy

Front of the eye disease leading to blindness in 50+ years of age

>250,000 patients with Repeat expansion in TCF4 in Western world

QR-504

For FECD3 repeat expansion in TCF4
No therapy available

Strong PoC

Strong preclinical PoC in human primary cell models. Development candidate selected

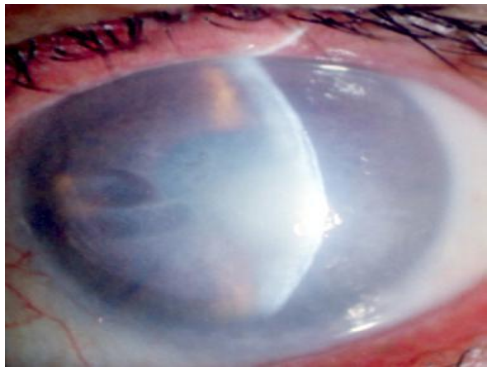
- ✓ RNA is established modality in eye
- ✓ Rapid delivery to corneal cells
- ✓ Strong preclinical proof of concept in human primary cell models

Next steps

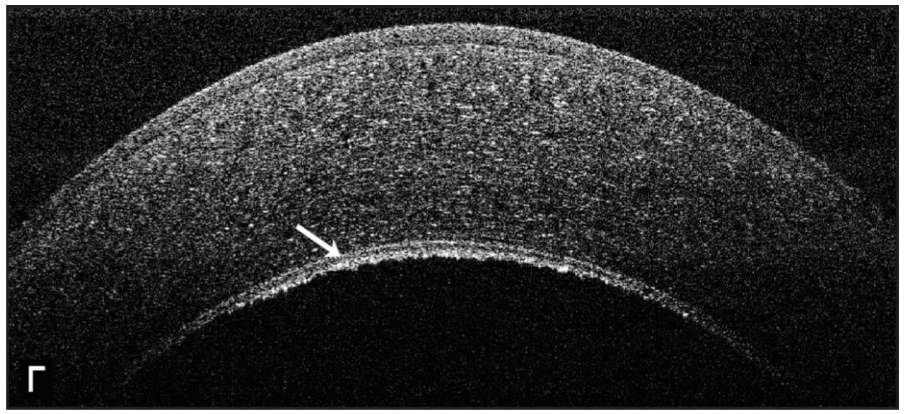
- Progression into development

Clinical phenotype: Fuchs Endothelial Corneal Dystrophy

Corneal edema and clouding



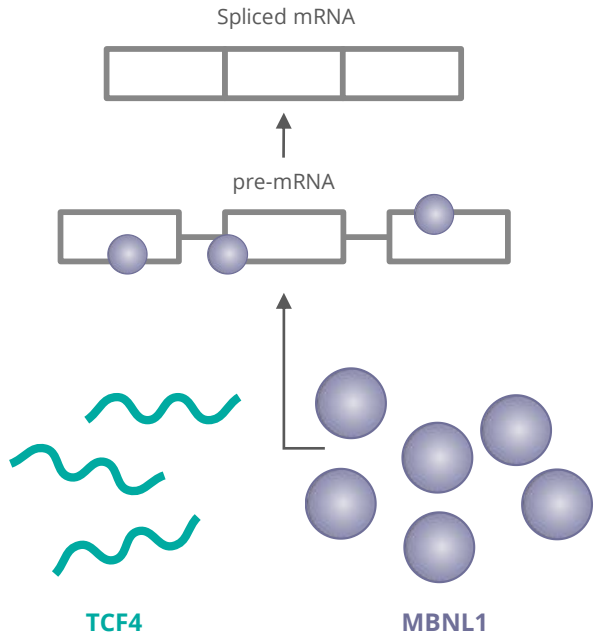
Guttae



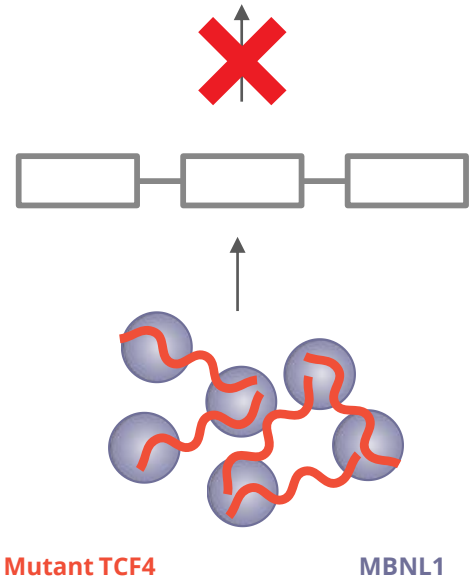
- Late onset (50-60 years) slowly progressing corneal dystrophy that usually affects both eyes
- Patients often awaken with blurred vision which improves during the day
- Visual acuity reduction
- Finally corneal swelling and clouding often requiring corneal transplantation

QR-504 for FECD3

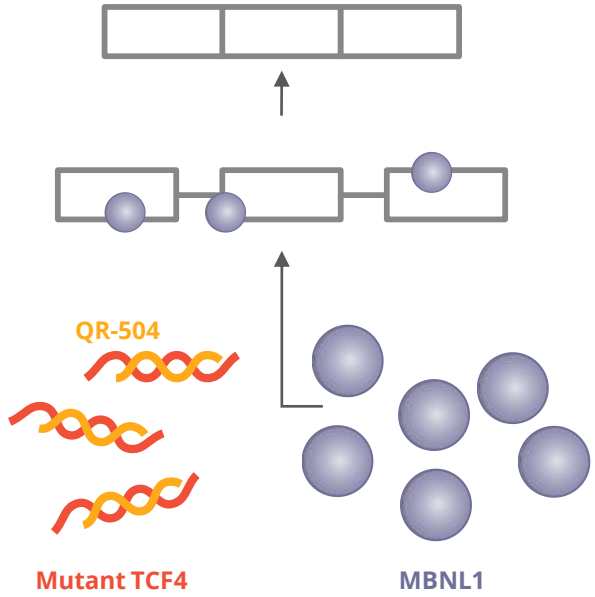
TCF4 repeat targeting for reduction of RNA foci



In healthy cells, MBNL1 protein regulates splicing of many RNAs

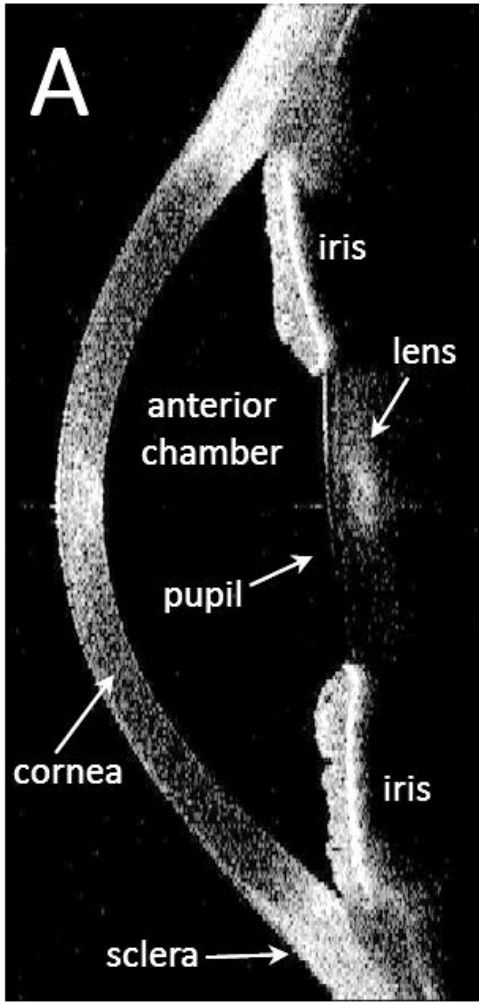


Mutated TCF4 RNA forms aggregates (foci) and sequesters MBNL1, disrupting splicing processes



QR-504 targets the TCF4 RNA (foci) and releases MBNL1 to enable correct splicing of RNA

QR-504 for FECD



QR-504 - Clinical Development

- 'Molecular PoC" in human corneal endothelial cells derived from FECD patients undergoing corneal transplant surgery

QR-504 - Asset Characterization

- Single stranded 21-mer RNA oligonucleotide
- Sequence and chemistry fully optimized.
- Chemically modified for stability and uptake
- Well understood MoA
- Designed to target nucleotide expansion in FECD3 patients caused by mutations in the TCF4 gene
- IVT administration, no detectable systemic exposure

QR-504 - Data

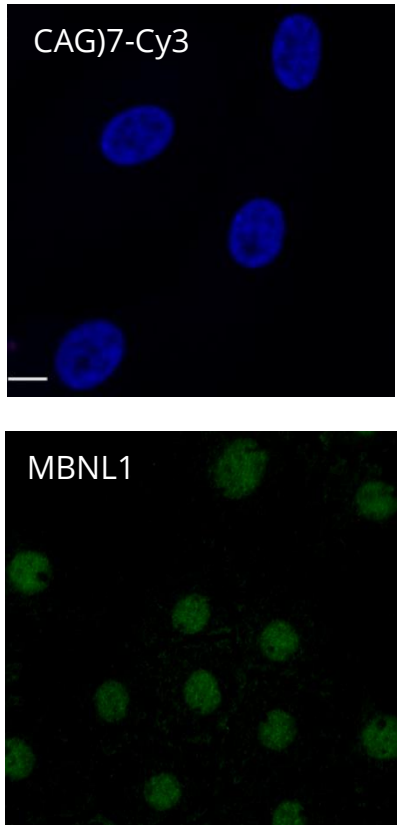
- Human TNR expanded TCF4 FECD3 CECs shown to have RNA foci and QR-504 treatment reduces foci
- Human TNR expanded TCF4 FECD3 CECs shown to have MBNL-1 sequestrated with RNA foci and QR-504 treatment releases MBNL-1
- Well understood MoA
- IVT administration shows QR-504 uptake in CECs from mouse and rabbit

FECD patients with TCF4 mutations have RNA foci

FECD is caused by toxic RNA aggregation and MBNL-1 sequestration

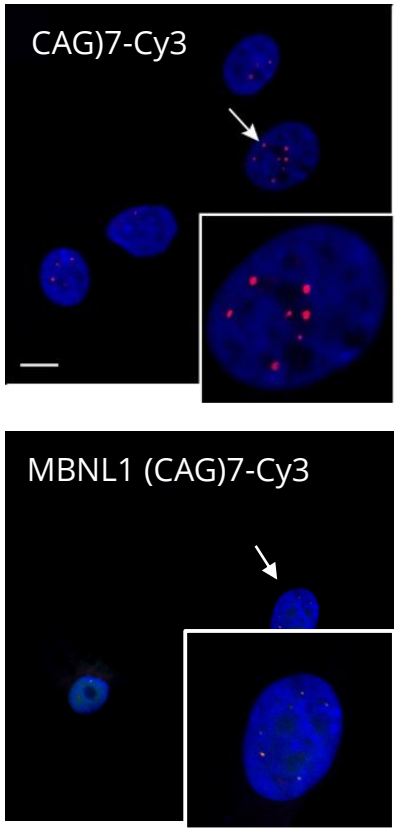
Control

TCF4 Free MBNL1



FECD

Mutant TCF4 MBNL1



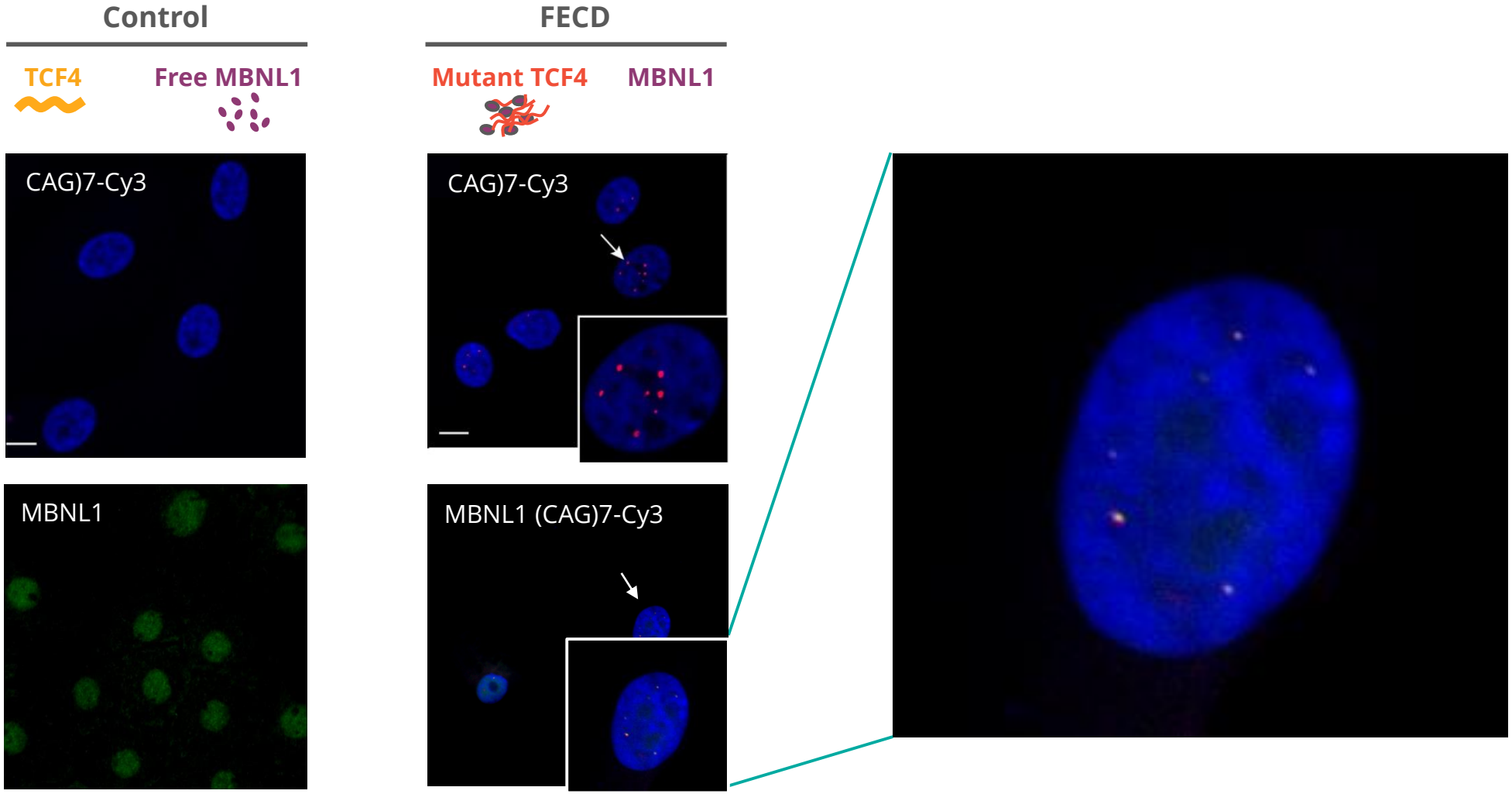
Article

Antisense Therapy for a Common Corneal Dystrophy Ameliorates *TCF4* Repeat Expansion-Mediated Toxicity

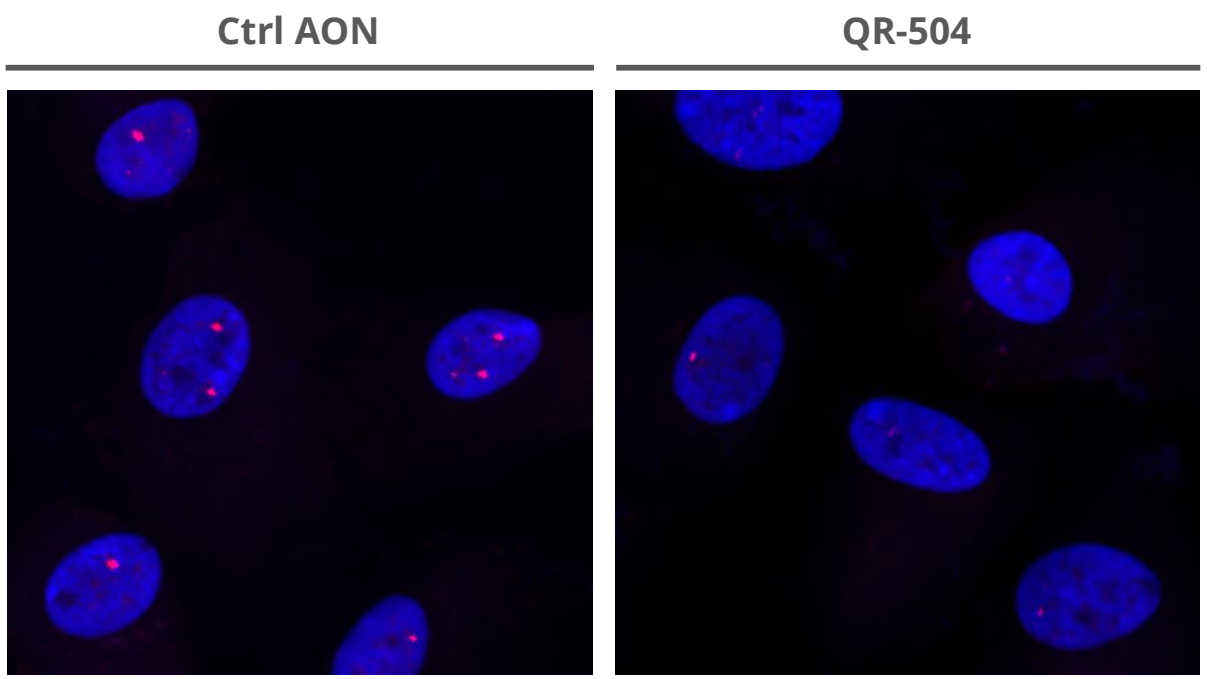
Christina Zarouchlioti,[1,8] Beatriz Sanchez-Pintado,[1,8] Nathaniel J. Hafford Tear,[1,8] Pontus Klein,[2] Petra Liskova,[3,4] Kalyan Dulla,[2] Ma'ayan Semo,[1] Anthony A. Vugler,[1] Kirithika Muthusamy,[1,5] Lubica Dudakova,[3] Hannah J. Levis,[6] Pavlina Skalicka,[3,4] Pirro Hysi,[7] Michael E. Cheetham,[1] Stephen J. Tuft,[1,5] Peter Adamson,[2,9] Alison J. Hardcastle,[1,9] and Alice E. Davidson[1,9,*]

FECD patients with TCF4 mutations have RNA foci

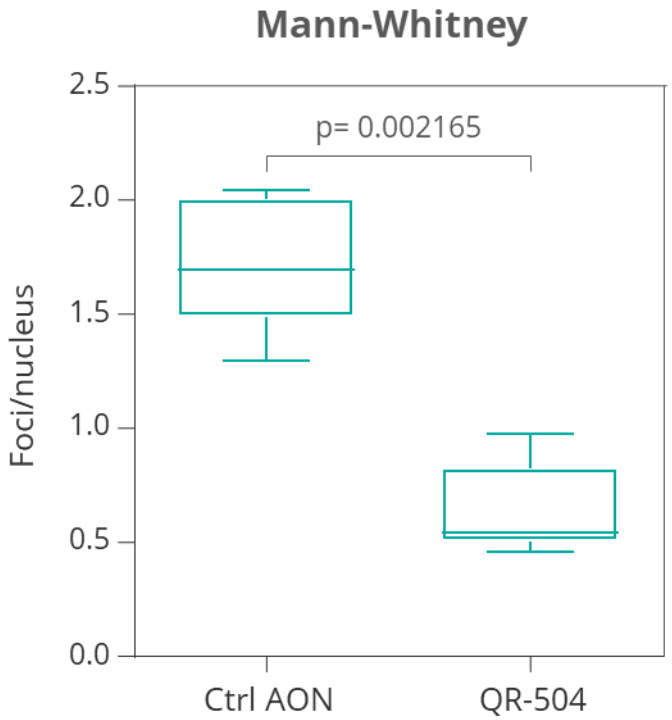
FECD is caused by toxic RNA aggregation and MBNL-1 sequestration



QR-504 reduces toxic foci

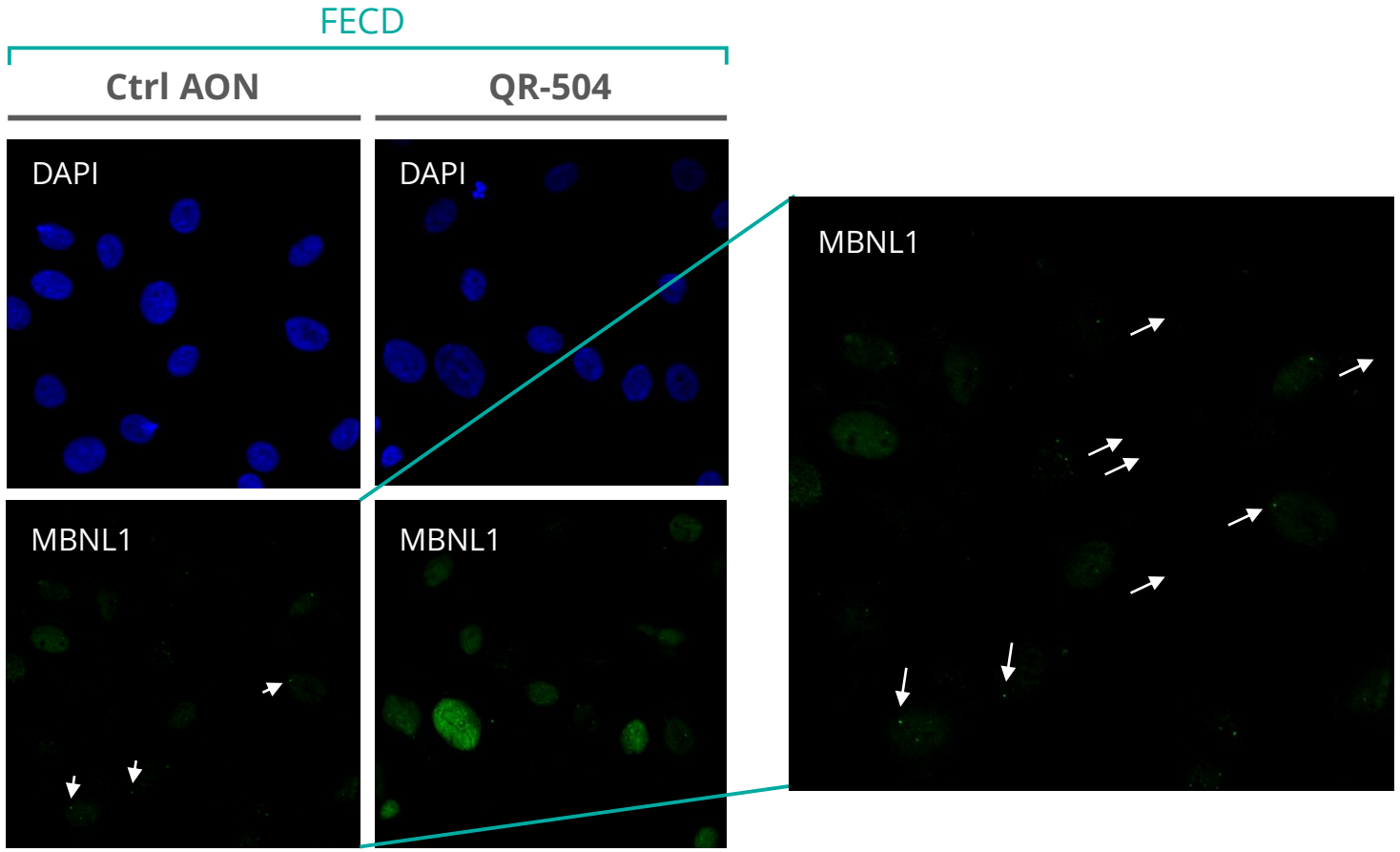


Patient #63, CTG 12/97

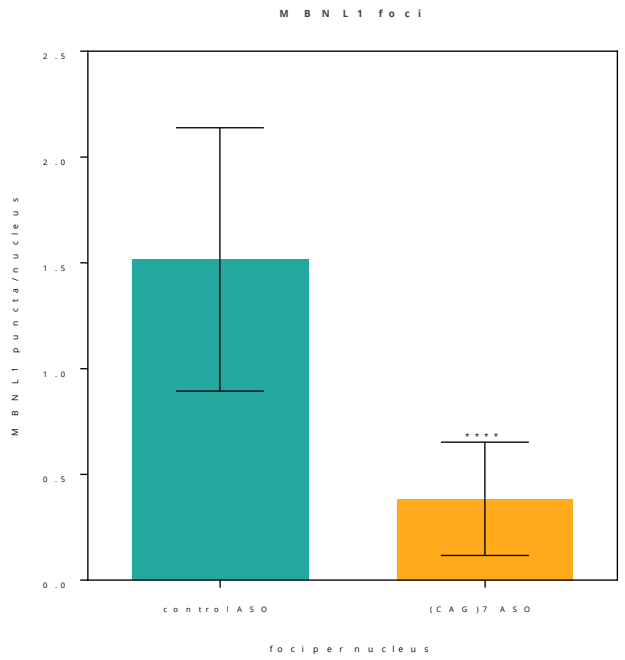


QR-504 reduces foci in patient CECs (N=6)

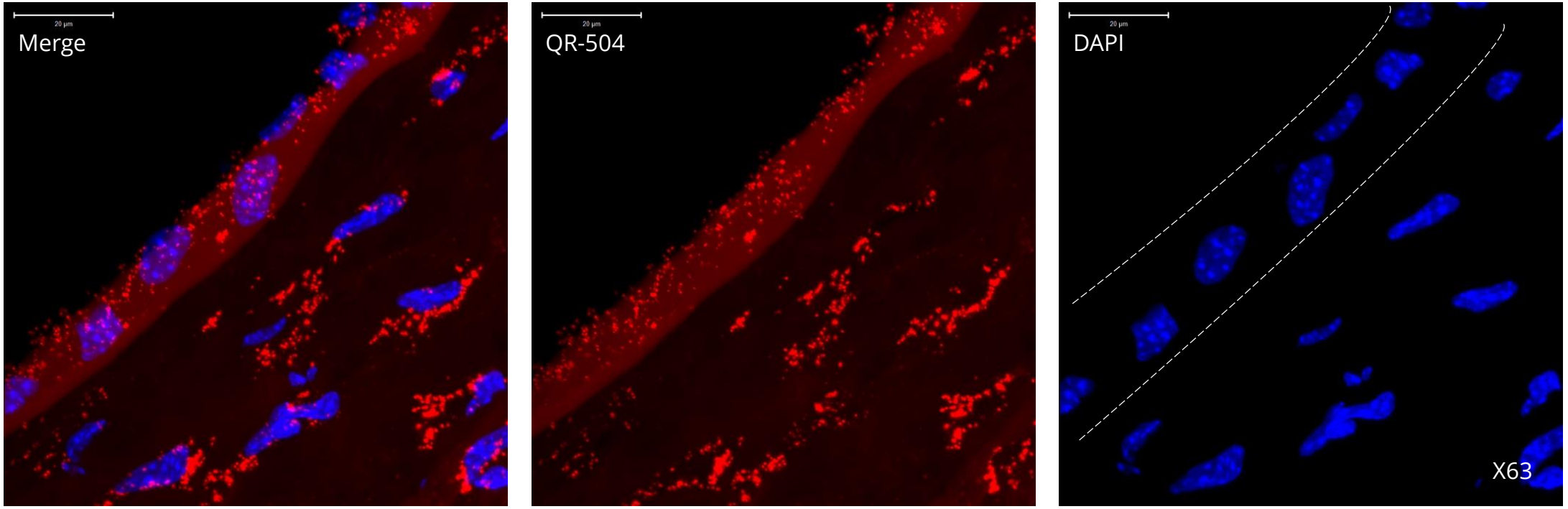
QR-504 reduces toxic foci and MBNL-1 sequestration



Patient #202, CTG 12,96



IVT administered QR-504 shows robust delivery to corneal endothelium



Cy3-labelled QR-504, 48h post dose, 10ug IVT dose

Ophthalmology: QR-504 for FECD

QR-504 reduces toxic foci

mRNA of toxic foci removed upon QR-504 treatment of primary corneal endothelial cells of FECD patients

QR-504 reduces sequestration of MBNL-1

MBNL-1 sequestration is reduced upon QR-504 treatment of primary corneal endothelial cells of FECD patients

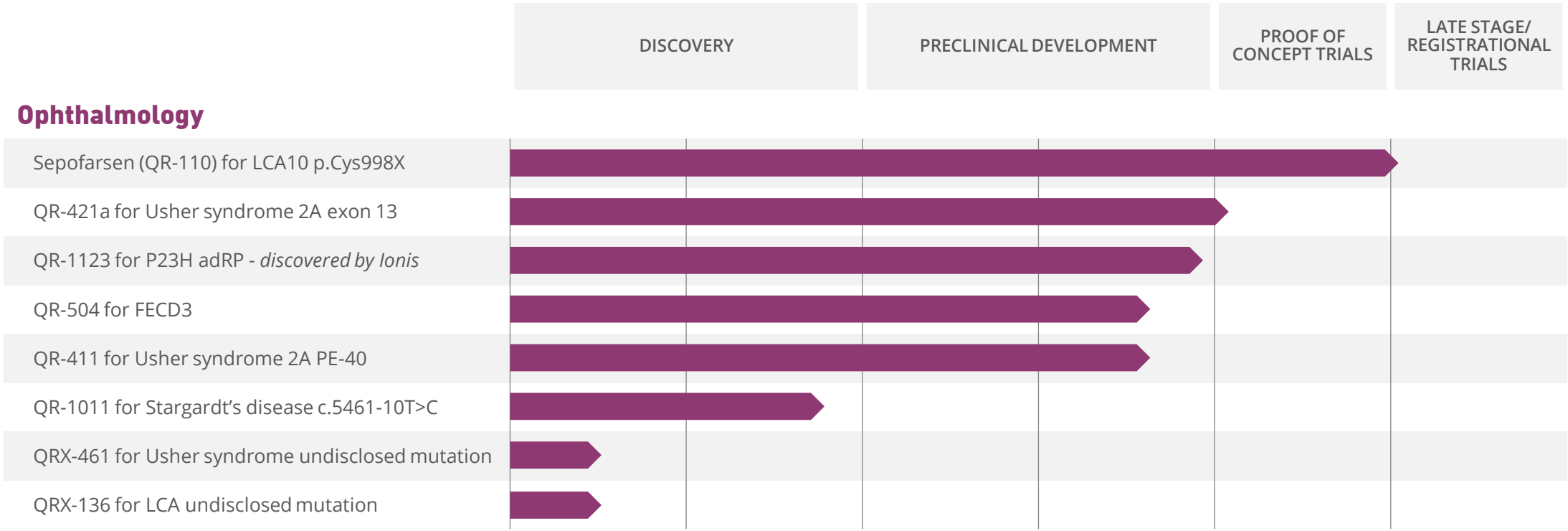
Local (intravitreal) delivery to the eye

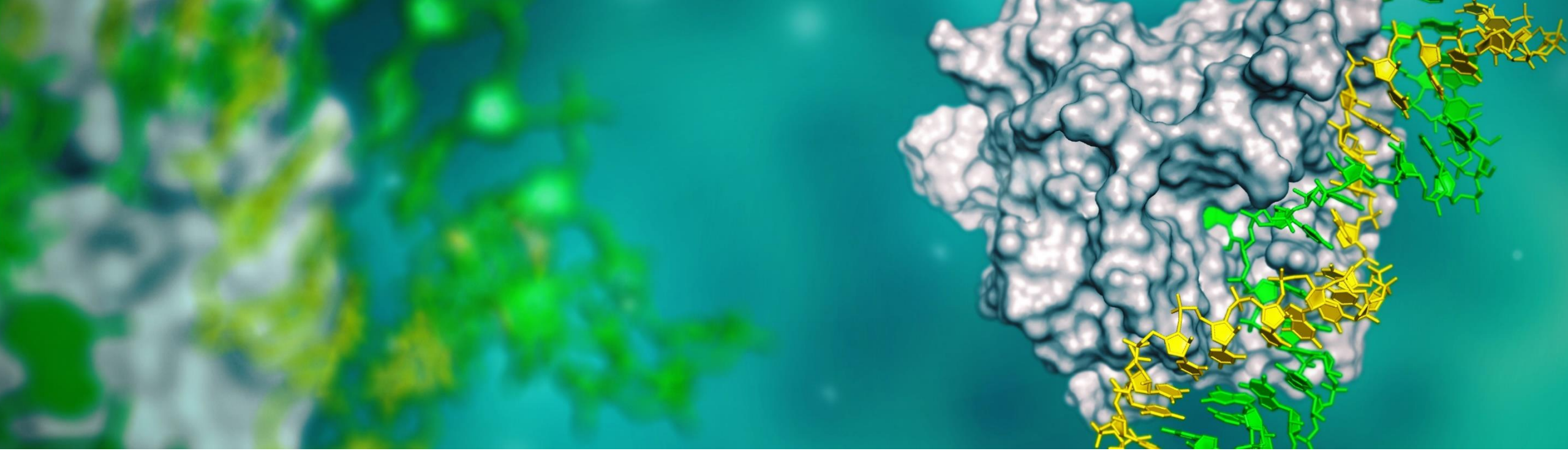
Eye well validated target for oligo's

Efficient delivery to corneal endothelium

Development

ProQR Ophthalmology pipeline





Innovation at ProQR

From LCA10 to 10 LCA's per year…

Gerard Platenburg, *Chief Innovation Officer*

Building from the current ophthalmology programs

Reaching patients beyond p.Cys998X mutation

Broad

Deep

CEP290, USH2A

Targeting additional CEP290, USH2A mutations which are not targeted by sepofarsen, QR-421a and QR-411

LCA

At least 24 genes other than CEP290 results in LCA

Retinitis Pigmentosa

More than 50 genes are implicated in Retinitis Pigmentosa

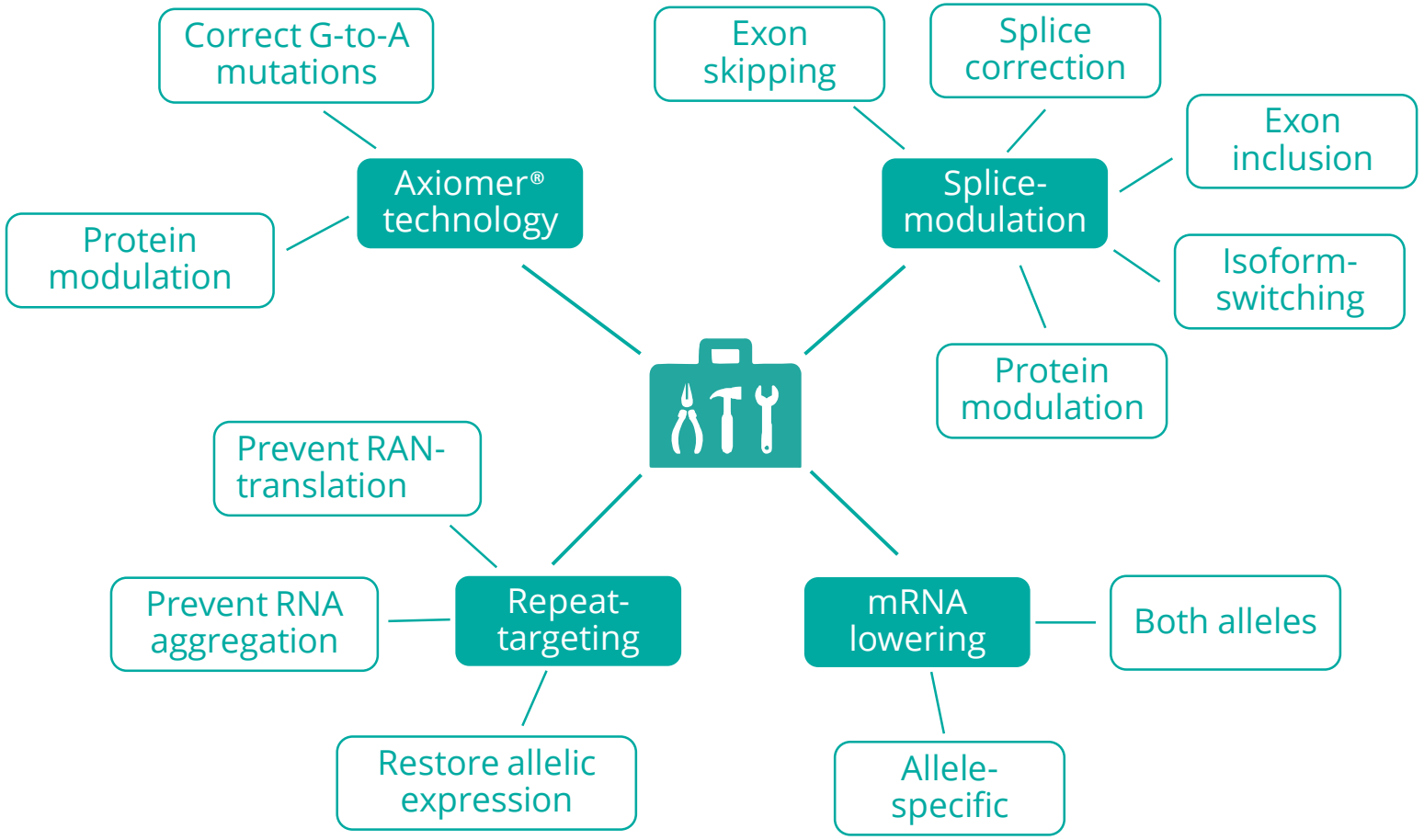
- Broadening beyond LCA and Ush2a
- ~300 inherited retinal disorders

RNA technology toolbox

One therapeutic modality using different MoAs

One modality- Variety of mechanisms

Antisense oligonucleotides, chemically modified to enhance uptake and increase stability



QRX-136 for LCA10

LCA10

Lose sight in first years of life

No therapy available

Undisclosed mutation in *CEP290* affecting **~500** patients in Western world*

QRX-136

Goal: Restore vision/ prevent vision loss in patients with LCA10

Locally administered in the eye. Routine intravitreal procedure

Anticipated infrequent dosing of 2 times a year

- ✓ RNA is established modality in eye
- ✓ Strong preclinical proof of concept

Next steps

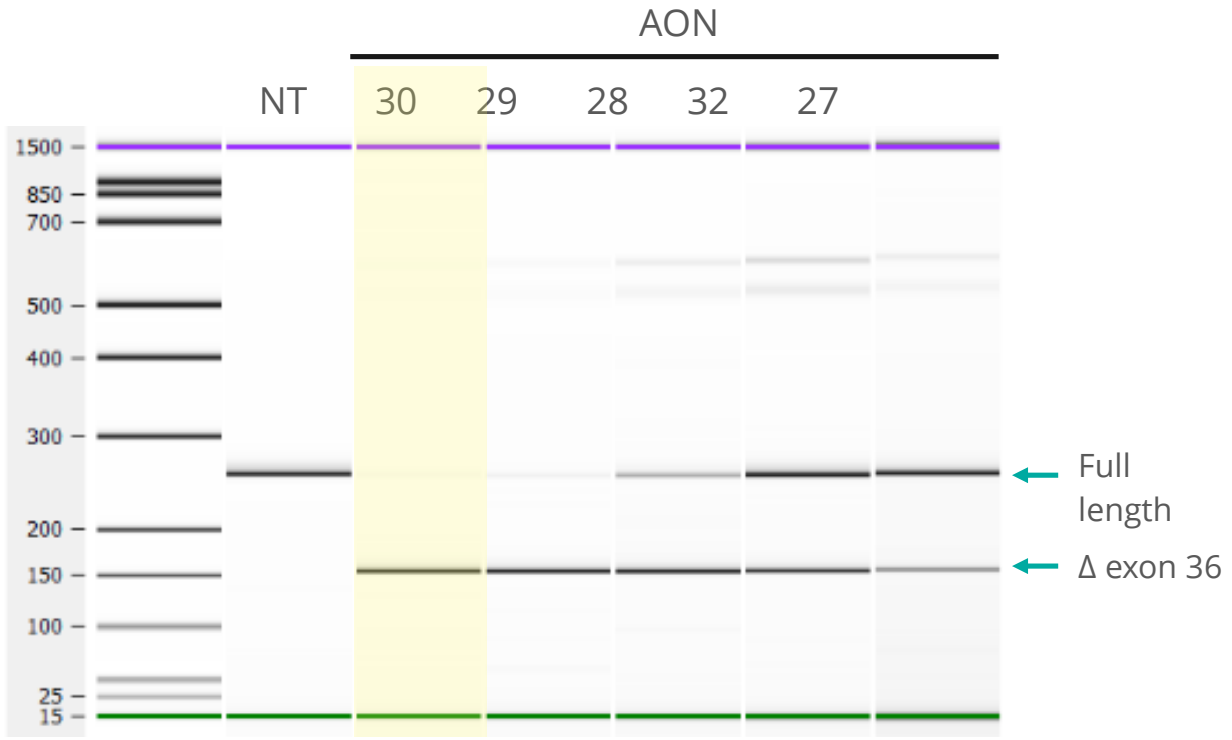
- Progression into lead selection
- Development following sepofarsen in well defined development plan

**Number based on initial prevalence assessment*

QRX-136 for LCA10

In vitro efficacy of AONs

- Several AONs identified that efficiently skip CEP290 exon 36
- Over 50% exon skip is observed
- Lead optimization is ongoing



QRX-461 for Usher syndrome

Designed to treat genetic eye disease in Usher syndrome 2a

Usher

Develop hearing loss and blindness in childhood and turn completely blind by mid adulthood

Undisclosed mutation in *USH2A* affecting **~5,000 - 10,000** patients in Western world*

QRX-461

No therapy available

Strong PoC

Strong preclinical PoC in vitro models.
Development candidate selection ongoing

- ✓ RNA is established modality in eye
- ✓ Strong preclinical proof of concept
- ✓ QRX-461is based on Axiomer® technology

Next steps

- Progression into lead selection
- Development following QR-421a and QR-411 in well defined development plan

**Number based on initial prevalence assessment*

Axiomer® technology

Therapeutic oligonucleotides for directing site-specific A-to-I editing by endogenous ADAR enzymes

Axiomer® Editing Oligonucleotides (EONs)

Oligonucleotide mediated targeted RNA editing

Unique RNA editing technology

Applicable to >20,000 disease-causing mutations

Similar capabilities as CRISPR, without the key risks

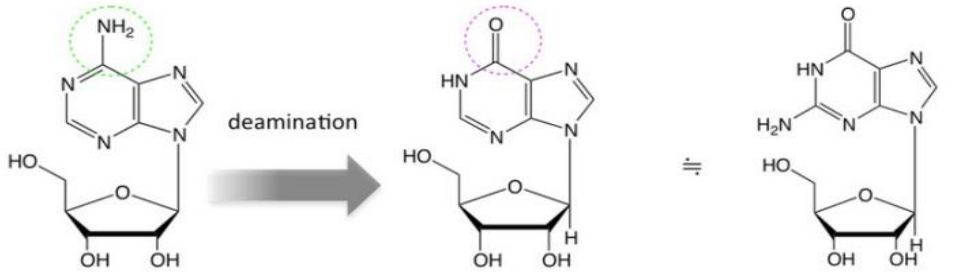
Brings clinical applicability of "editing" in reach

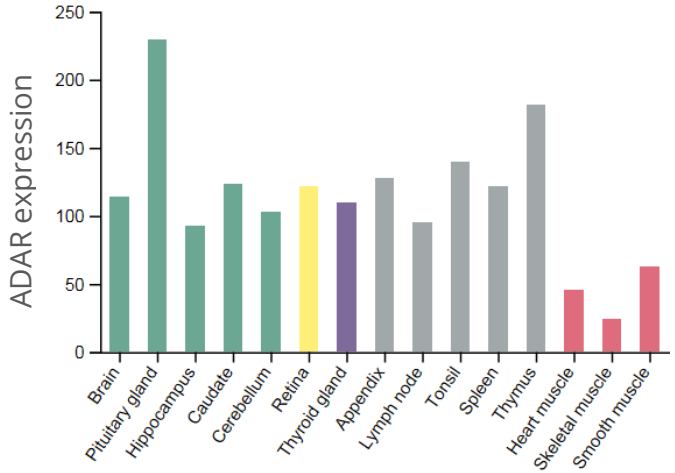
IP fully owned ProQR far ahead of competition

In-vitro PoC established in multiple disease models

A-to-I editing: Therapeutic opportunity

The most prevalent editing event in human tissues





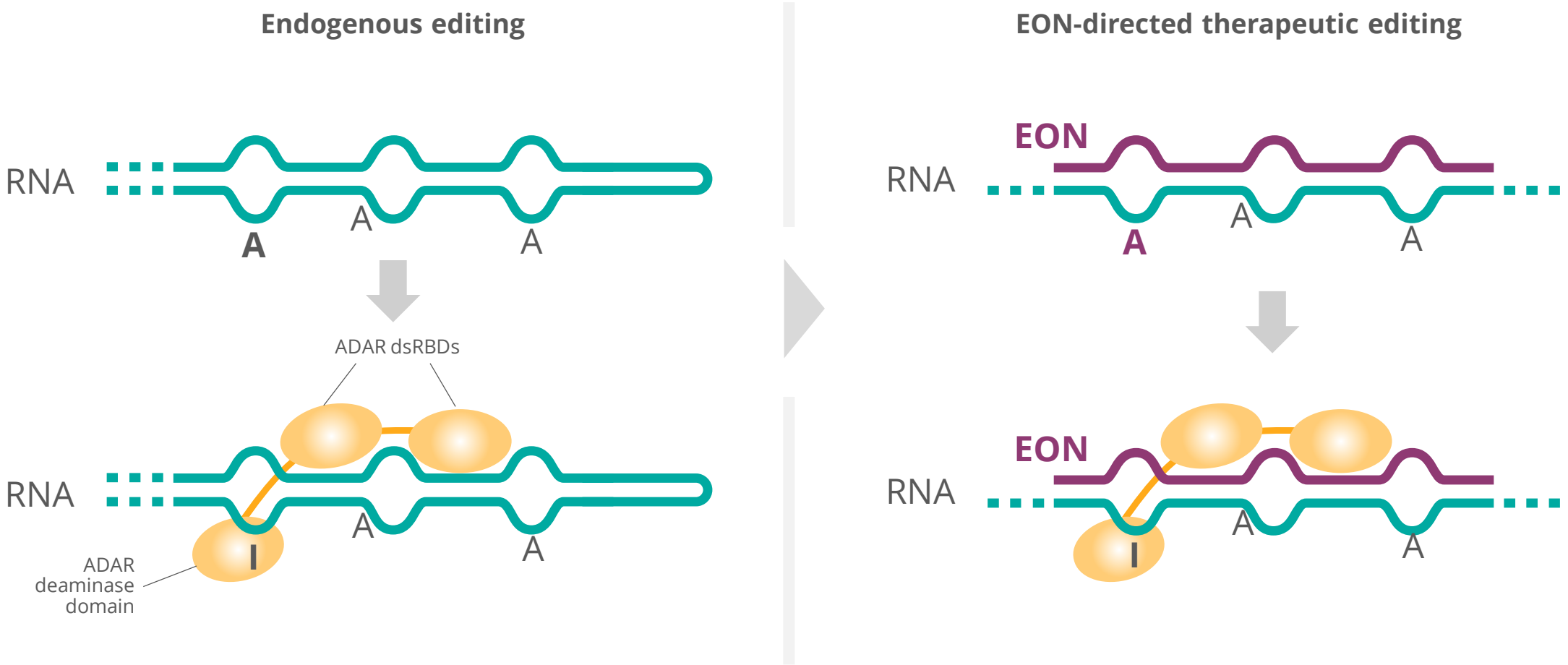
Adapted from Protein atlas

- No sequence dependence
- 4 million A-to-I sites in the human transcriptome, both in coding and non-coding RNAs
- Extent of editing similar in most human tissues, making therapeutic editing feasible in all disease areas

- ADAR1 and ADAR2 expressed in retina
- >20,000 G-to-A disease causing mutations in genome
- >1,100 G-to-A disease causing mutations in retinal genes
- ~90 G-to-A mutations found in Ush2a

EONs designed for targeted editing

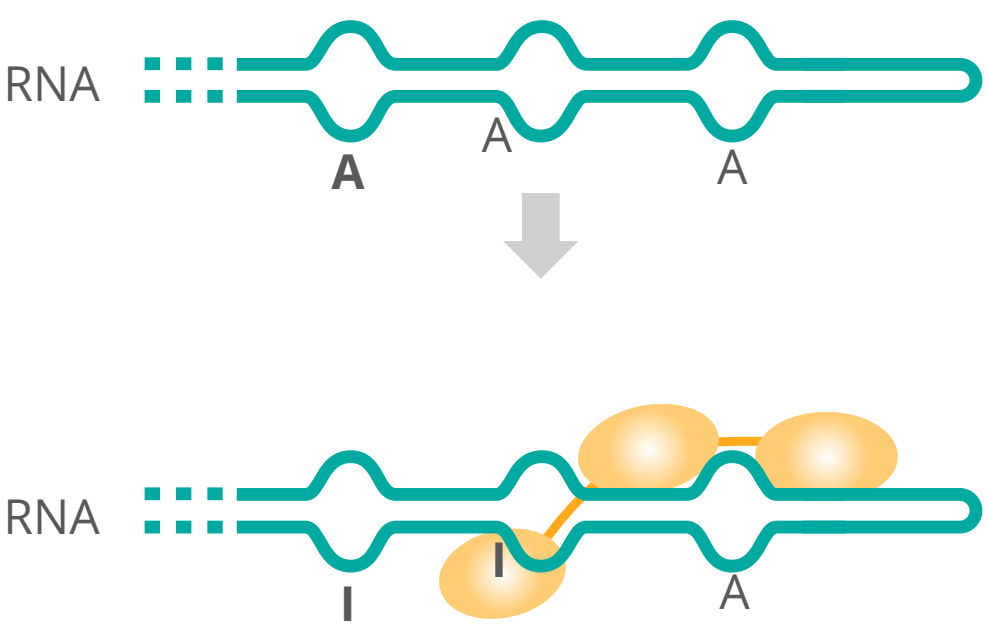
ADAR deaminates target A in EON-target RNA helix



EONs designed for targeted editing

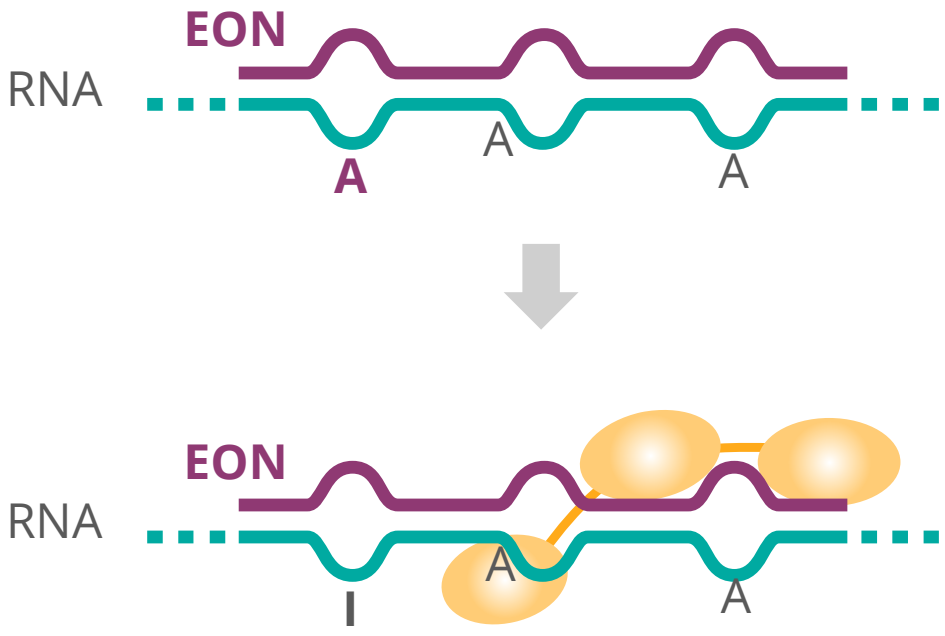
Advantage over RNA guides: Specificity

Endogenous editing



Editing site with RNA guides is flexible

EON-directed therapeutic editing



Editing site with EONs is precise:
No off-target editing even if ADAR shifts

Structural basis for nt modifications

ADAR binding and catalysis require different modifications

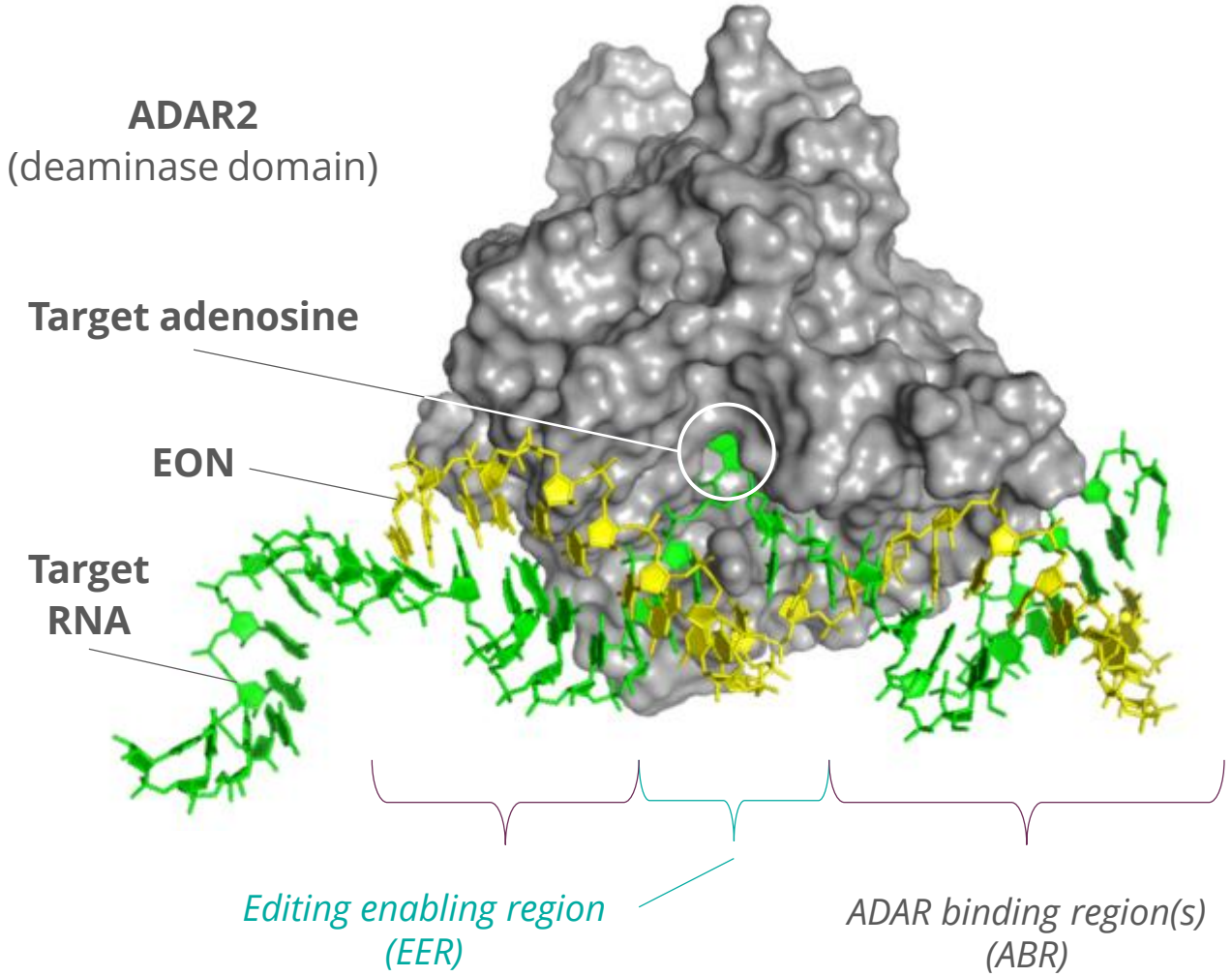
ADAR binding region

- Modifications compatible with ADAR binding, but which do not fit in the catalytic center

Editing enabling region

- Modifications that fit into the catalytic center

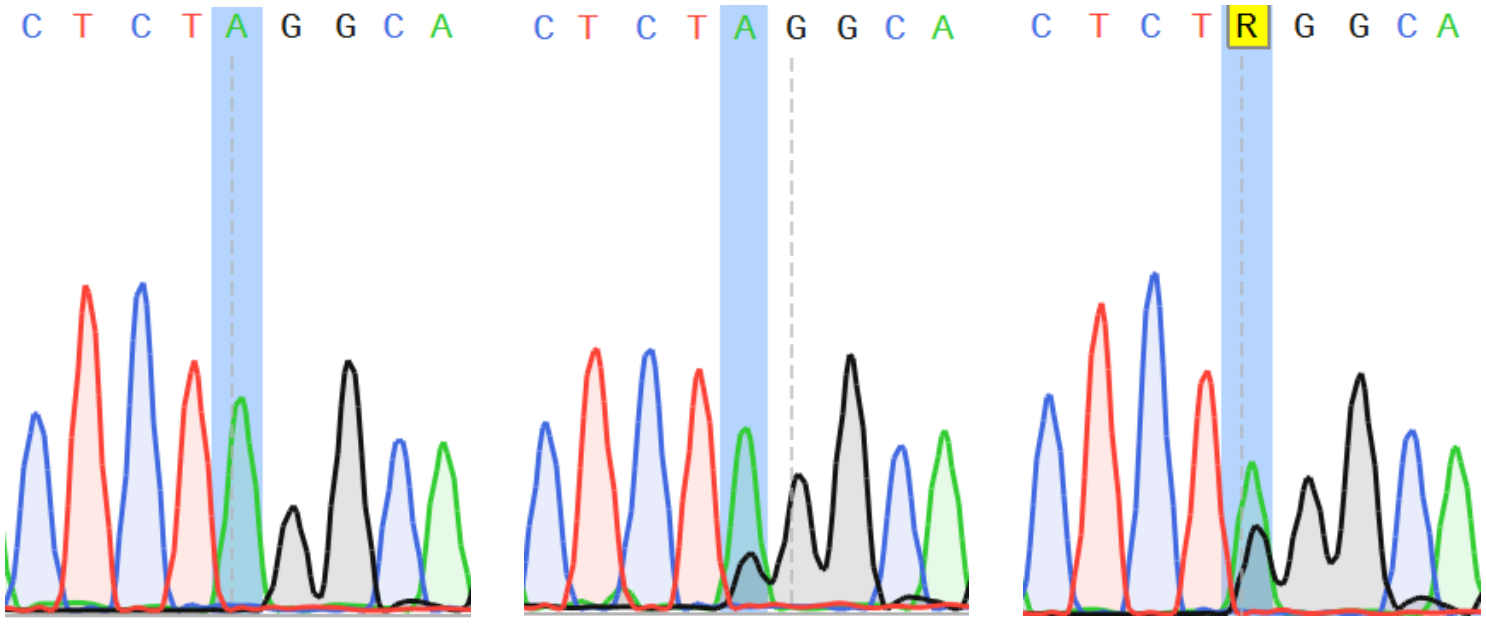
Structural modelling provides a **basis for further optimization of EONs**



EONs edit *Idua* mRNA *in vitro*

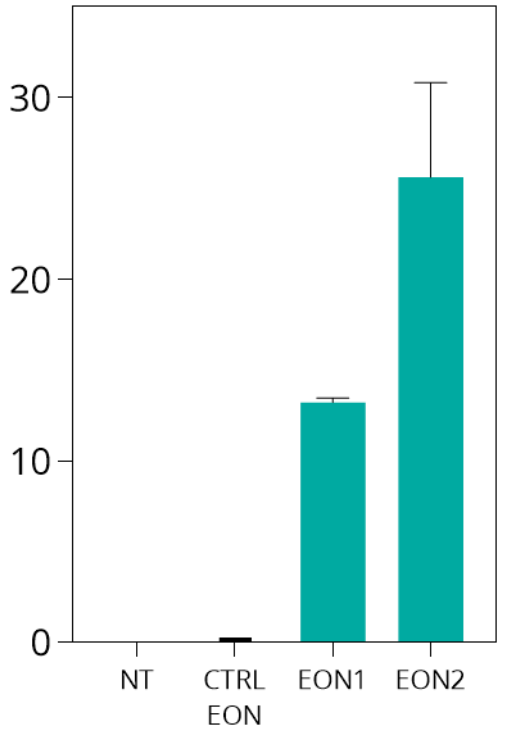
Idua W392X reporter construct in MEF cells with endogenous ADAR

Sanger sequencing



Non-treated | EON 1 (100 nM) | EON 2 (100 nM)

Digital droplet PCR (% edited *Idua* mRNA)



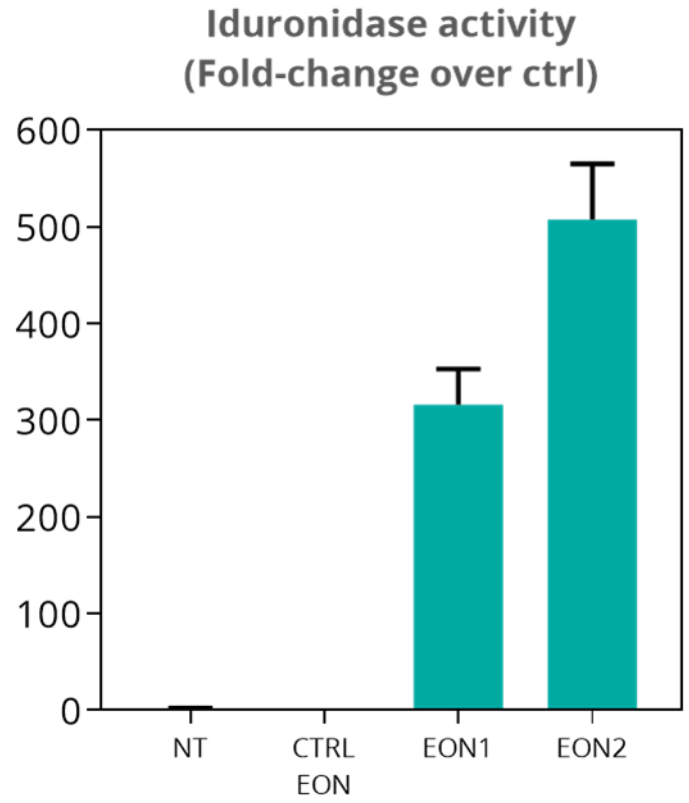
EONs restore iduronidase *in vitro*

Idua W392X reporter construct in MEF cells with endogenous ADAR

Proteins from EON-treated cells

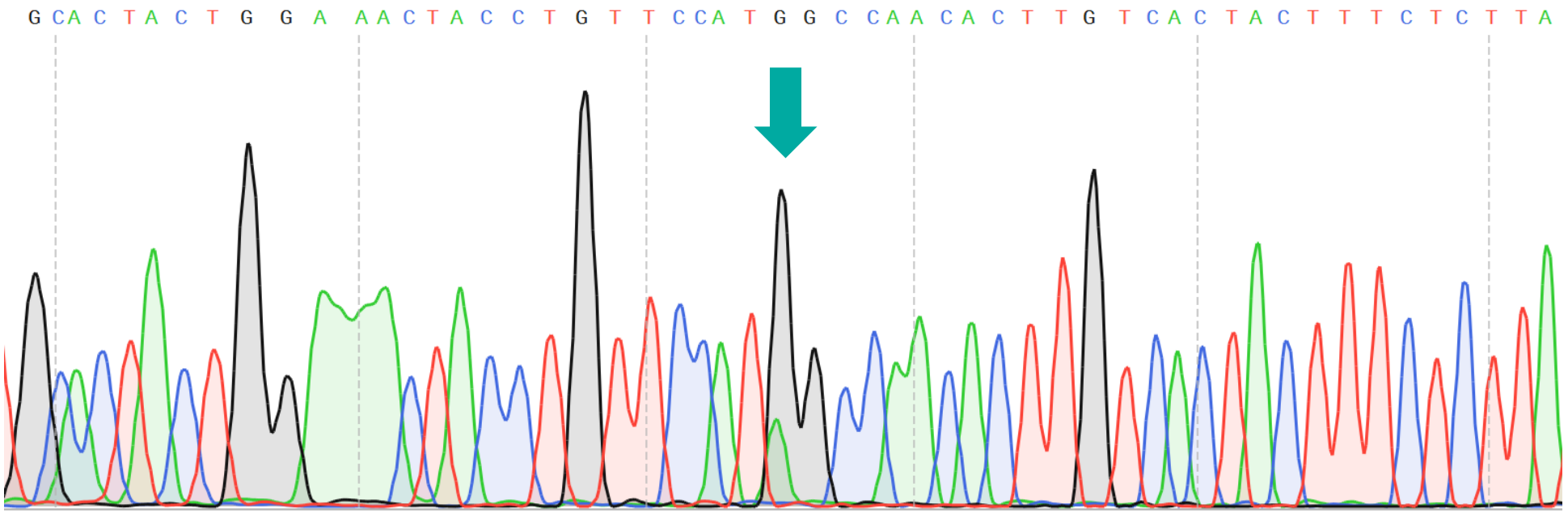
Incubation with fluorescent iduronidase substrate analog

Fluorescent readout



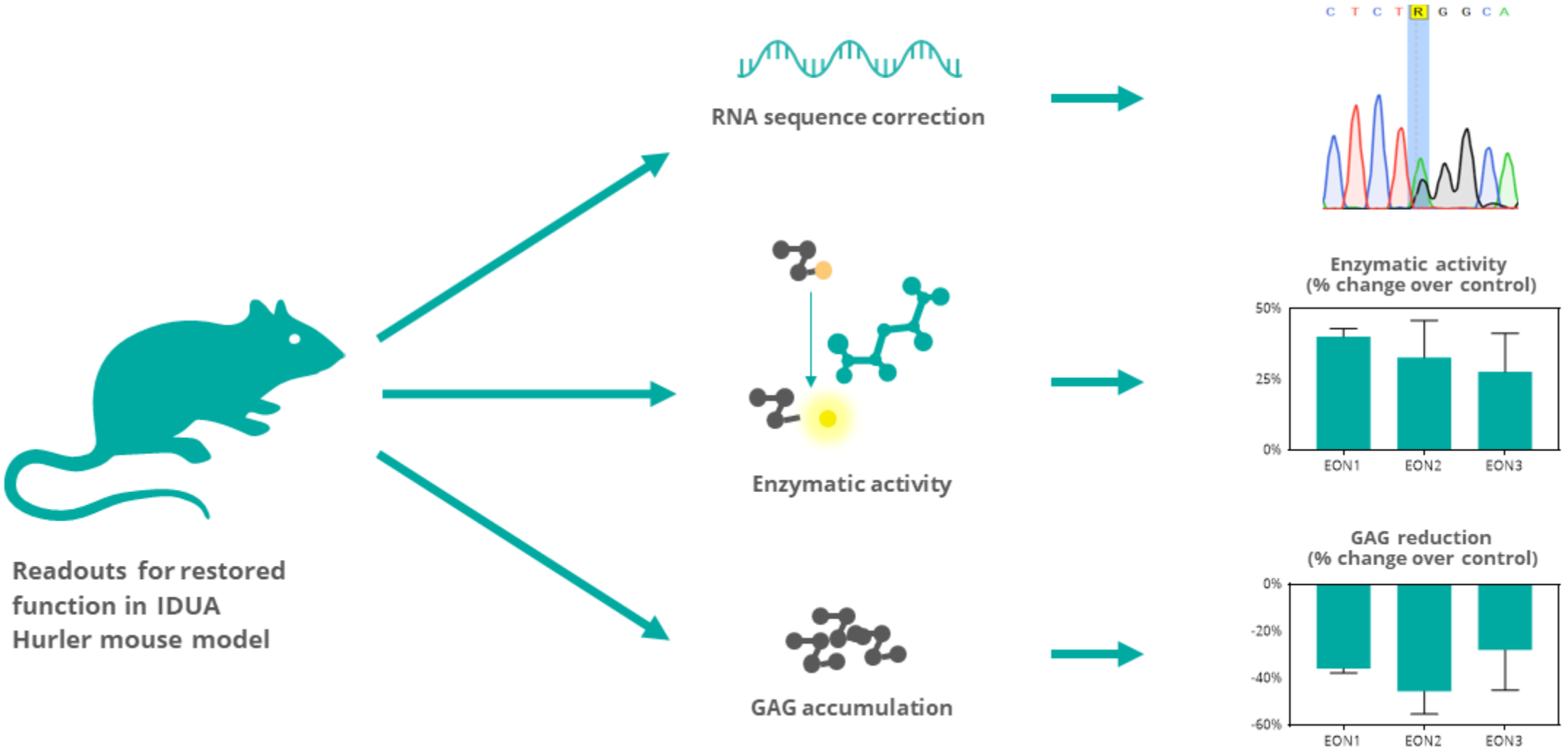
Nt modifications ensure specificity

Editing only observed at the target adenosine, even when overexpressing ADAR in cells



- 100 nM EON transfection with GFP W57X reporter and ADAR1 **overexpression**
- Readout by Sanger sequencing of the RT-PCR product
- ~85% editing at target A; **no off-target editing observed**

PoC in Hurler mouse model for targeted editing



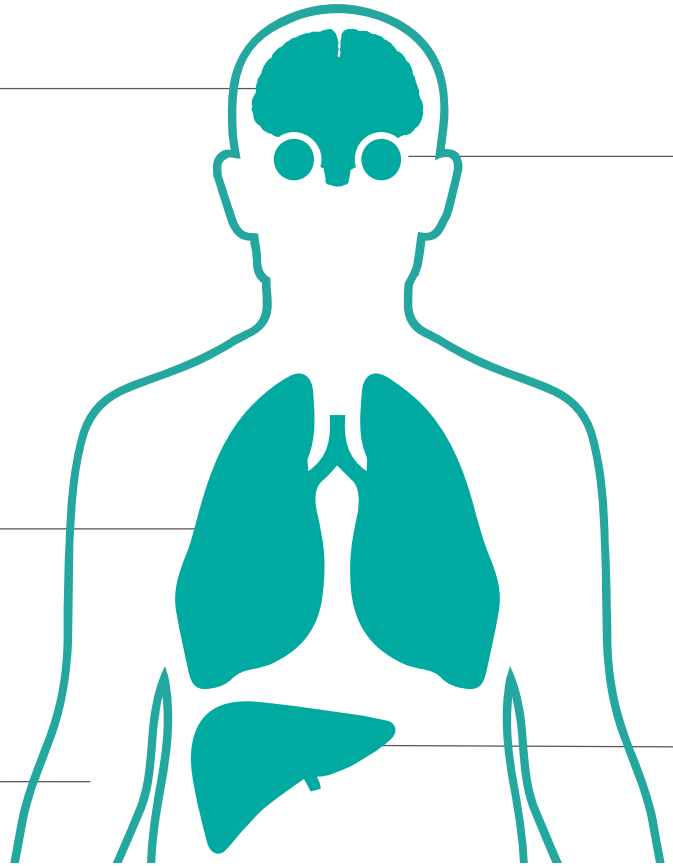
Axiomer® is widely applicable

Examples of ophthalmic targets

CNS (>500 targets)
- Parkinson's Disease VIII
- Hurler Syndrome
- Alzheimer's Disease
- Huntington's Disease
- Parkinson's Disease II
- Fragile X syndrome

Lung (>300 targets)
- Cystic Fibrosis non-dF508
- Primary ciliary dyskinesia
- Surfactant Metabolism Dysfunction
- ABCA3 deficiency
- Familial Pulmonary Fibrosis

Skin (>500 targets)
- Albinism
- Dystrophic Epidermolysis Bullosa
  Junctional Epidermolysis Bullosa
- Darier disease
- Epidermolysis Simplex



Ophthalmology (>1,100 targets)
- Leber's Congenital Amaurosis 4
- Usher's syndrome
- Fuchs Endothelial Corneal Dystrophy
- Retinitis Pigmentosa type 3
- Stargardt's Disease
- Primary Congenital Glaucoma

Liver (>1,500 targets)
- Alpha-1 Antitrypsin Deficiency
- Factor V Deficiency
- Transthyretin-related hereditary amyloidosis
- Wilson disease
- Hereditary Hemochromatosis
- Ornithine Transcarbamylase deficiency
- Hemophilia B
- Pompe Disease

QRX-461 for Usher syndrome

Designed to treat genetic eye disease in Usher syndrome 2a

Usher

Develop hearing loss and blindness in childhood and turn completely blind by mid adulthood

Undisclosed mutation in *USH2A* affecting **~5,000 - 10,000** patients in Western world*

QRX-461

No therapy available

Strong PoC

Strong preclinical PoC in vitro models.
Development candidate selection ongoing

- ✓ RNA is established modality in eye
- ✓ Strong preclinical proof of concept
- ✓ QRX-461is based on Axiomer® technology

Next steps

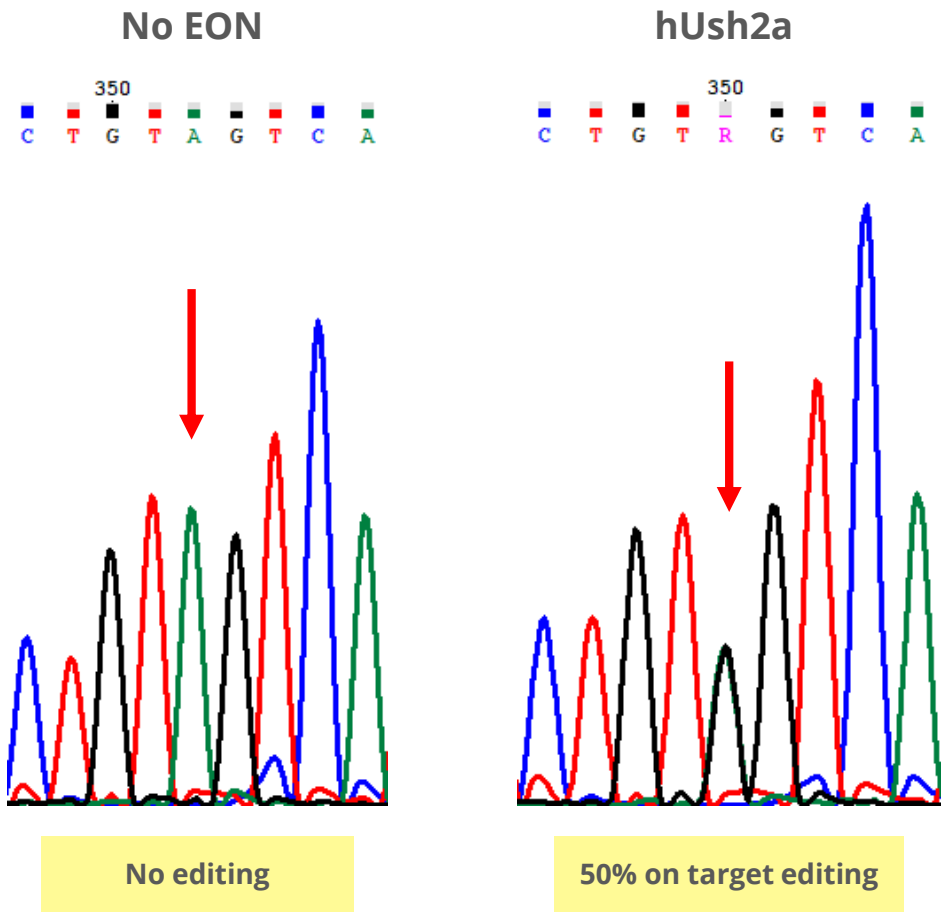
- Progression into lead selection
- Development following QR-421a and QR-411 in well defined development plan

*Number based on initial prevalence assessment

QRX-461 corrects G-to-A mutation

In vitro efficacy of AONs

- Several EONs designed for Usherin exon 61
- Up to 50% editing is observed
- Optimization is ongoing



Q&A

ProQR®

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JANUARY 29, 2019, NEW YORK