ProQR®

ProQR R&D DAY

JUNE 15, 2017, NEW YORK

Forward looking statements

This presentation contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this presentation, including but not limited to, statements regarding our strategy, future operations, future pre-clinical and clinical trial plans and related timing of trials and results, research and development, future financial position, future revenues, projected costs, prospects, therapeutic potential of our products, plans and objectives of management, are forward-looking statements. The words "aim," "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

Forward-looking statements represent our management's beliefs and assumptions only as of the date of this presentation. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. The forward-looking statements contained in this presentation reflect our current views with respect to future events, and we assume no obligation to update any forward-looking statements except as required by applicable law. These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including those that may be described in greater detail in the annual report filed on Form 20-F for the year ended December 31, 2016 that we have filed with the U.S. Securities and Exchange Commission (the "SEC") and any subsequent filings we have made with the SEC. We have included important factors in the cautionary statements included in that annual report, particularly in the Risk Factors section, and subsequent filings with the SEC that we believe could cause actual results or events to differ materially from the forward-looking statements that we make.

Our mission and strategy

Treat Genetic Diseases

- ProQR was founded to find a treatment for CF
- Less than 10% of genetic diseases have a treatment
- Creating treatments for severe rare diseases where we can have a big impact

Build strong foundation

- Experienced team with proven track record
- Top-notch science and collaborators
- Broad IP estate

RNA therapeutics

- Elegant & highly targeted approach
- Emergent RNA field with 5 approved products
- Established modality through >20 years of experience (delivery, safety, manufacturing, etc.)

Created valuable pipeline

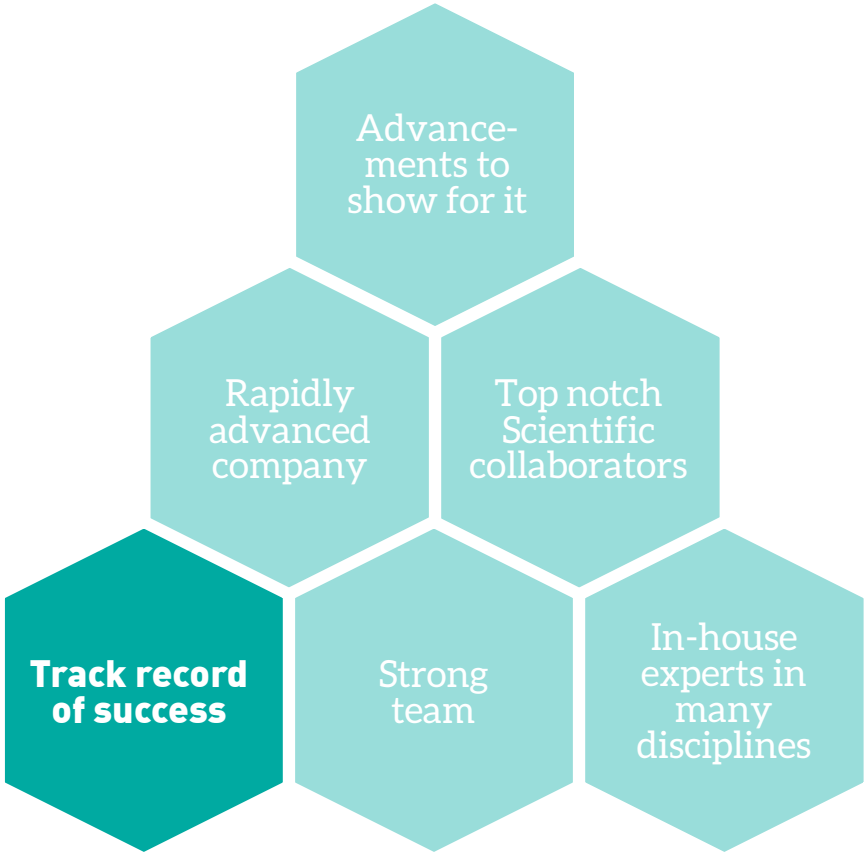
- Diversified product pipeline
- Focused on high unmet medical need and accelerated development pathways

Build a sustainable business

- Best-in-class products
- Achievable commercial strategy in rare diseases
- Drive shareholder value

ProQR: 2012 - now

Strong foundation under solid company



Track record of success

Dinko Valerio

Crucell

Henri Termeer

genzyme

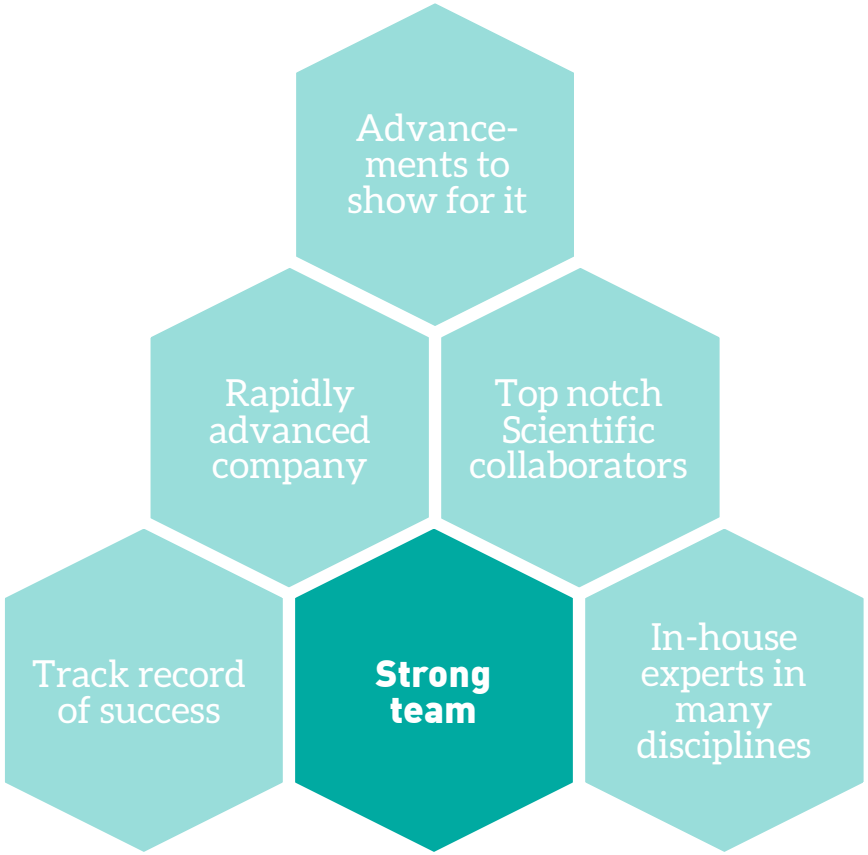
James Shannon

gsk

NOVARTIS

ProQR: 2012 – now

Strong foundation under solid company



Management team

Daniel de Boer
Chief Executive Officer

Noreen Henig
Chief Medical Officer

Gerard Platenburg
Chief Innovation Officer

Smital Shah
Chief Financial Officer

René Beukema
Chief Corp. Development Officer & General Counsel

Robert Cornelisse
Chief People & Organization

David Rodman
Chief Development Strategy Officer

Supervisory board

Dinko Valerio
Chairman

James Shannon

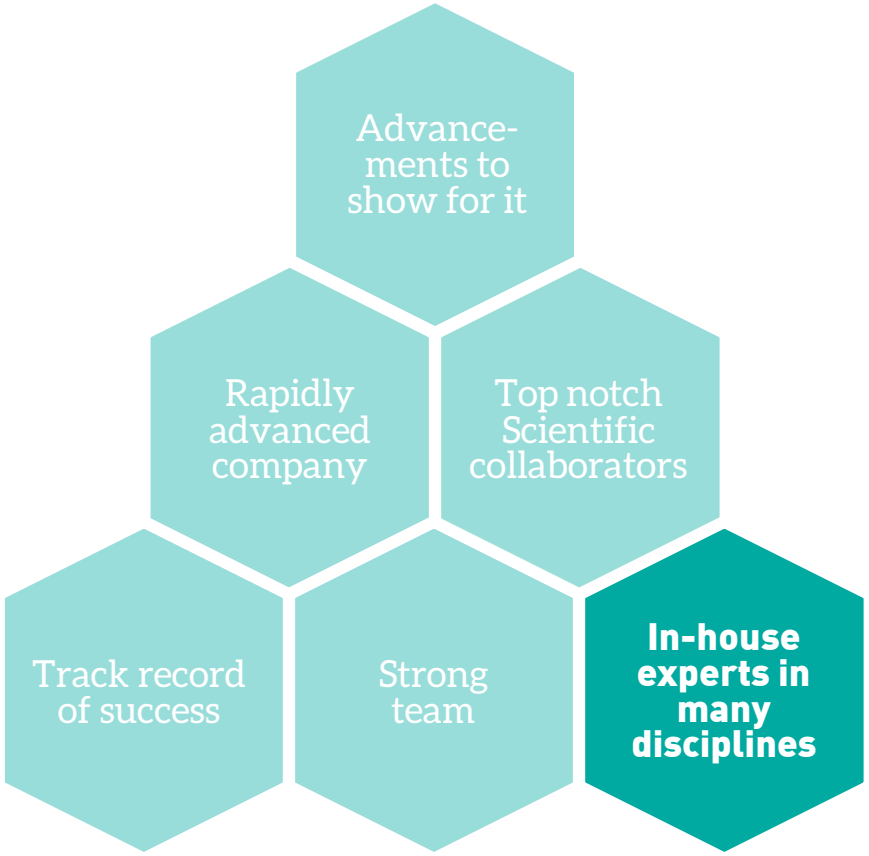
Antoine Papiernik

Alison Lawton

Paul Baart

ProQR: 2012 - now

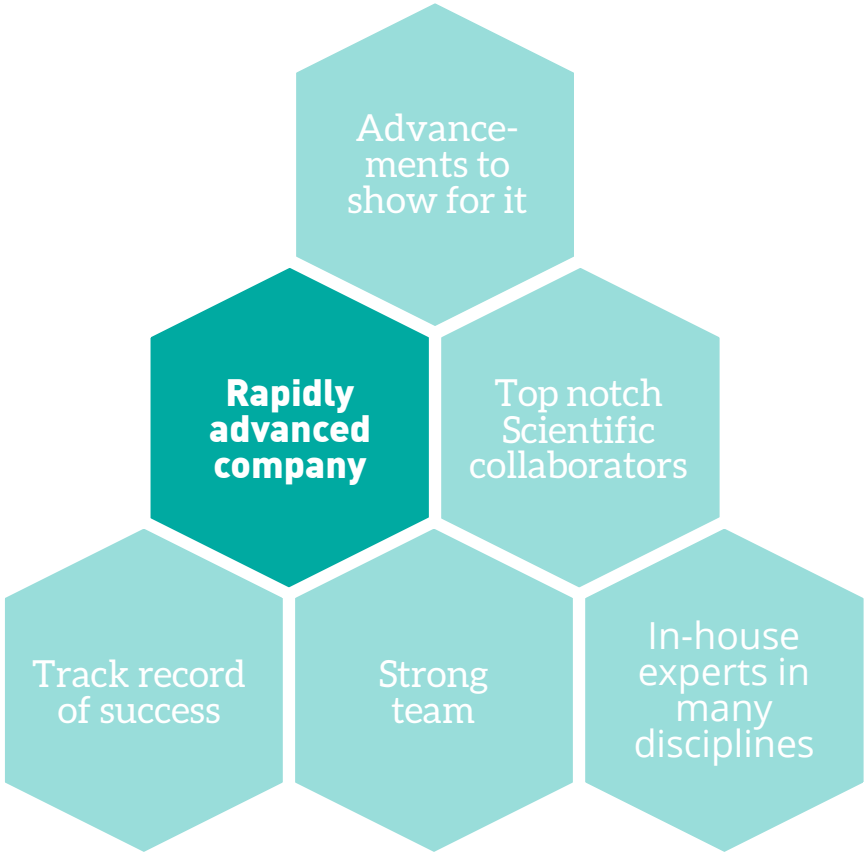
Strong foundation under solid company



150 employees in EU and US work on discovering and developing therapies

ProQR: 2012 – now

Strong foundation under solid company

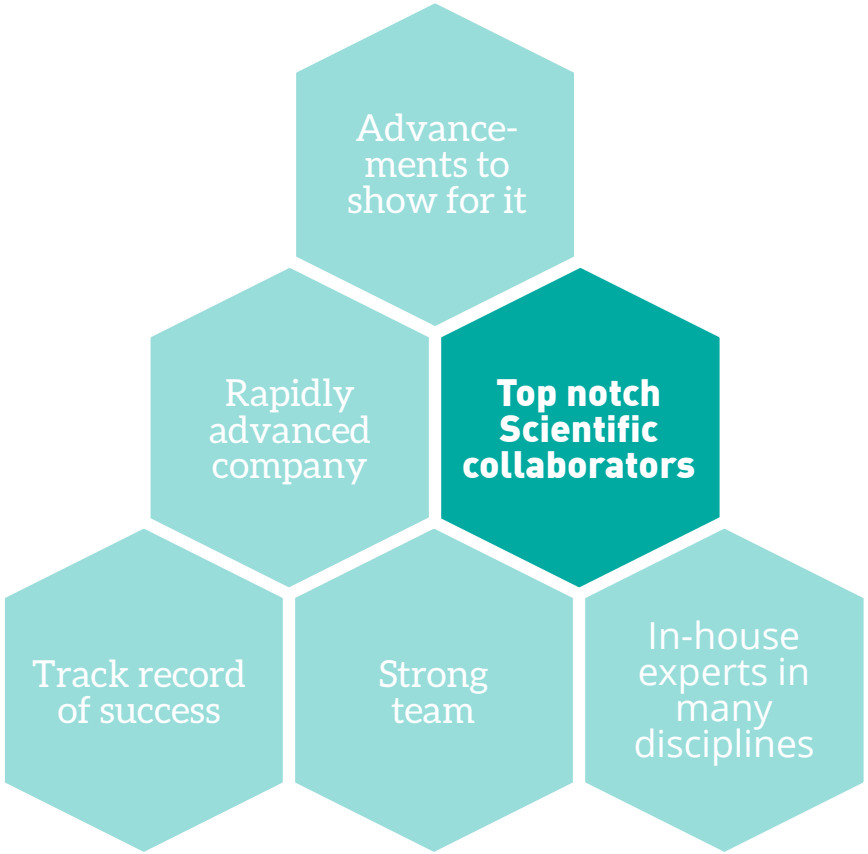


Rapidly advanced entrepreneurial company

- **2014:** In 2 years from foundation to Nasdaq IPO, raising ~$200M
- **2015:** In 3 years from IP to start global clinical trial
- **2016:** In 4 years to clinical PoC in lead product
- Unique operating model with product focused biz units enabling rapid development of company and pipeline

ProQR: 2012 - now

Strong foundation under solid company

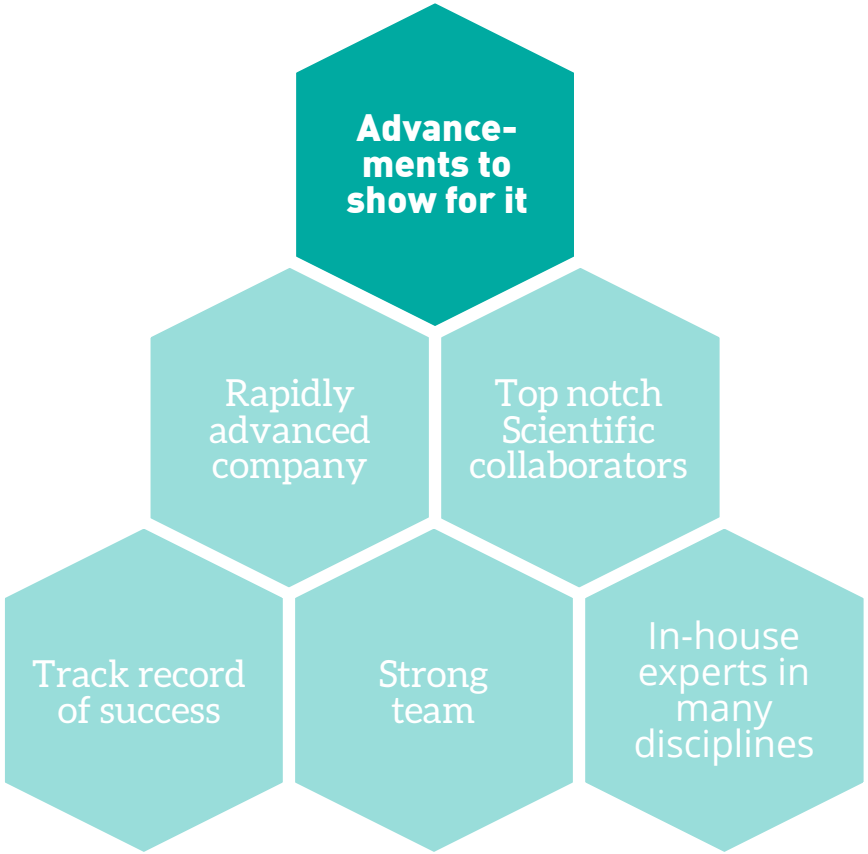


Top notch science and collaborators

Massachusetts General Hospital · Stanford University · UAB · University of Bristol · UCL · Rosalind Franklin University of Medicine and Science · Leids Universitair Medisch Centrum · The University of North Carolina at Chapel Hill · Radboud Universiteit Nijmegen · Foundation Fighting Blindness · debra · Cystic Fibrosis Foundation

ProQR: 2012 – now

Strong foundation under solid company



Positioned for success

- **QR-010 (CF) with positive clinical data**
  - Phase 1b top line data expected in September 2017
  - Phase 2 to start in 2018
- **QR-110 (LCA 10) IND clearance for clinical trial**
  - IND cleared, first patient to be dosed soon, trial completed in 2018
- **QR-313 (DEB) clinical trial to start in 2018**
  - Clinical trial to start and readout in 2018
- **Discovery pipeline that has the potential to deliver new IND every year**
  - Ophthalmology, Axiomer®
- **Cash position (end Q1 2017): € 52.1M**
  - Runway into Q3 2018

Therapeutic Strategy

Patient centric
Best-in-class high impact products for patients in need

Well understood causality
Single gene defect leading to disease manifestation

Local delivery
Feasible delivery route to target organ

Genetic rare diseases
Limited treatment options, viable commercial strategy

RNA therapy
Highly specific approach for a wide range of mutations

Accelerated development
Accelerated development strategies to treat patients faster

Key programs in ProQR pipeline

Cystic Fibrosis

QR-010 for F508del cystic fibrosis

- ✓ Positive clinical data in NPD biomarker study
- Phase 1b study top line data expected in September 2017

Inherited blindness

QR-110 for LCA10

Pipeline

- QRX-411 for Usher syndrome
- QRX-421 for Usher syndrome
- QRX-504 for FECD
- QRX-1011 for Stargardt's Disease

Debilitating skin disorders

QR-313 for DEB

Pipeline

- QRX-323 for DEB
- QRX-333 for DEB
- QRX-343 for DEB

Highlights Innovation pipeline

Axiomer®

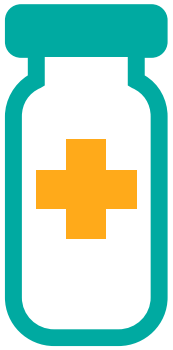
- Novel RNA editing platform technology
- Direct ADAR to make specific edits in RNA
- >20.000 G>A mutations

QR-010

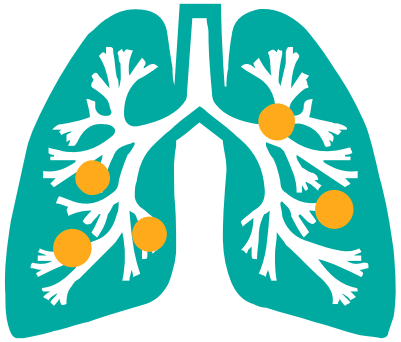
Cystic fibrosis due to F508del mutation

Presenter: **Noreen Henig**

Cystic fibrosis due to F508del mutation

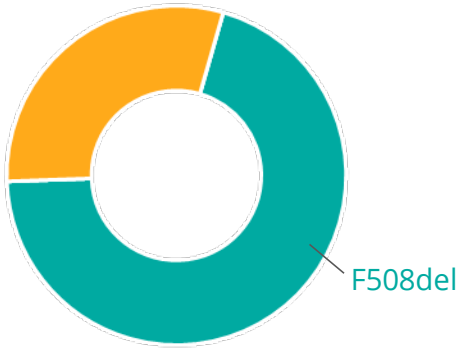


High unmet medical need



Lung & other organs

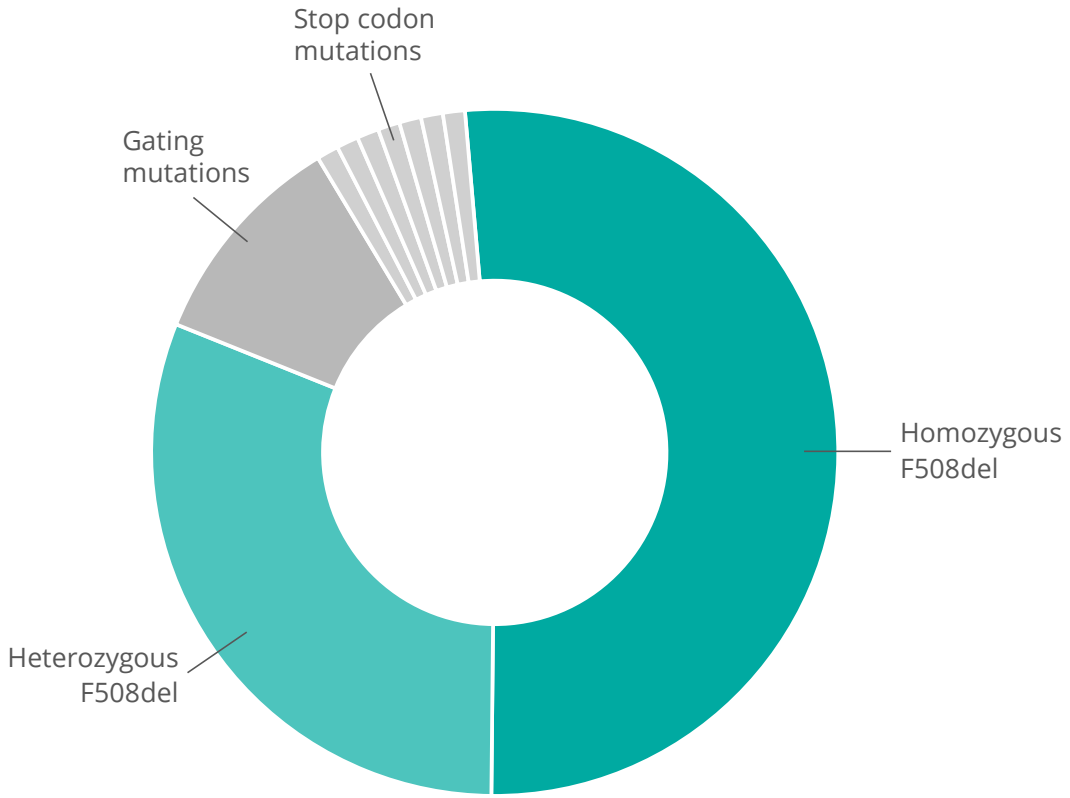
Limited life expectancy of 27 years



Most common mutation affects ~65,000 patients

Cystic Fibrosis is a heterogeneous population

- **More than 2,000 CFTR mutations known**
- **F508del patients**
  - Variable drug response within F508del population
  - Expected that several different therapies are needed to treat different subgroups of F508del population
- **Beyond QR-010 for F508del**
  - RNA therapies have potential to target stop-codon mutations



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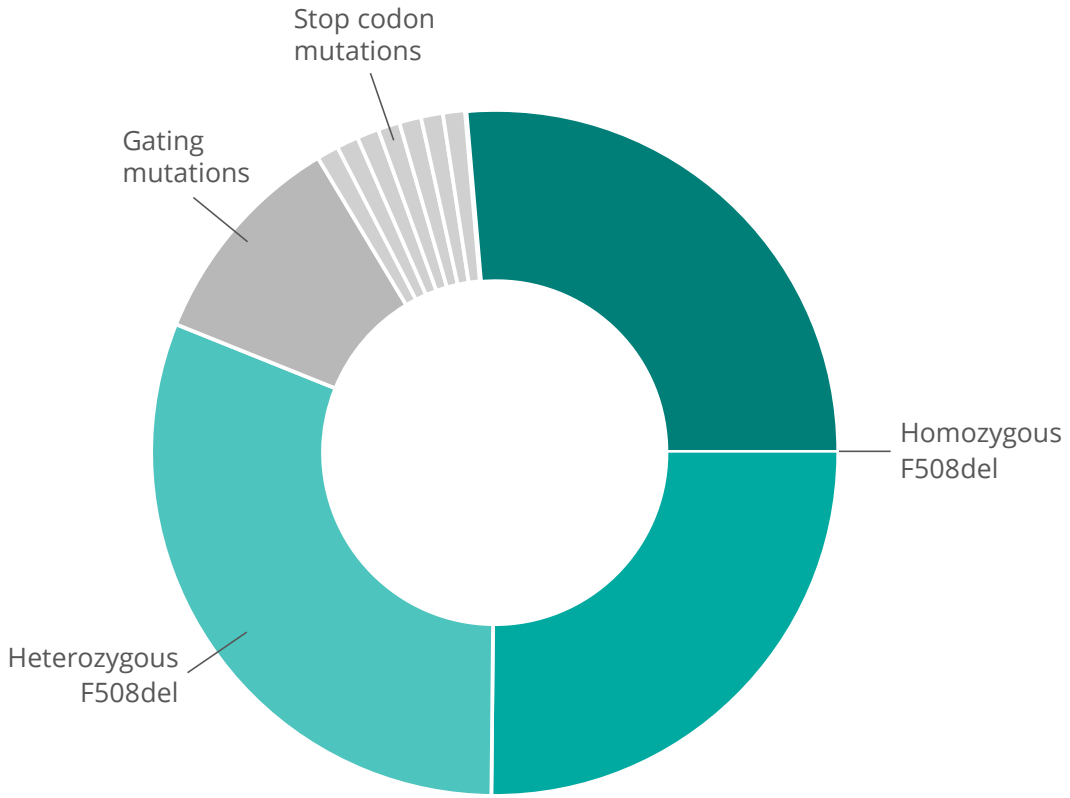


QR-010 for F508del cystic fibrosis

Differentiating product profile

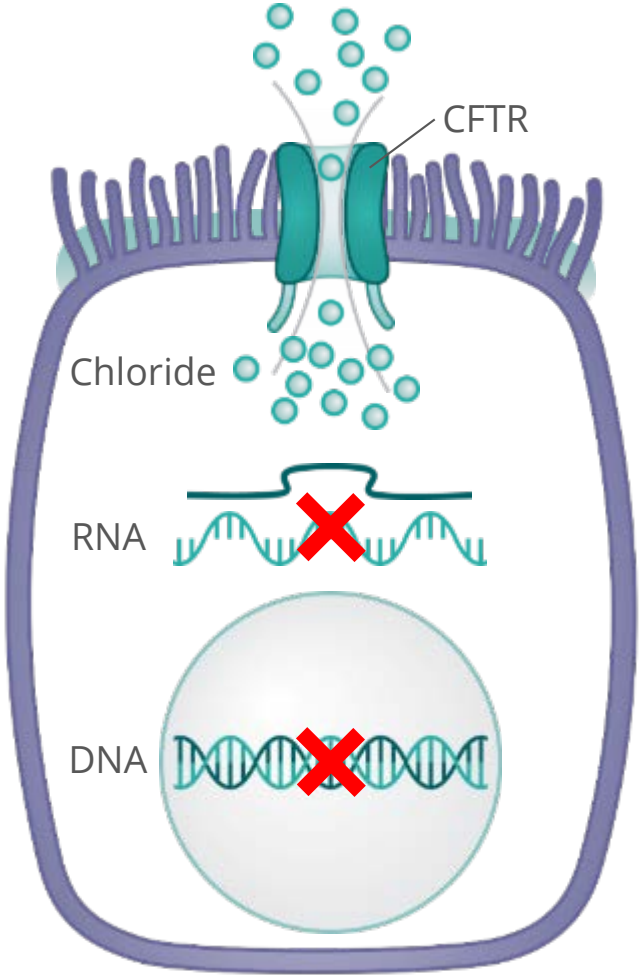
INHALED DRUG
for lung delivery and systemic uptake

SINGLE AGENT for F508del
to treat underlying cause of disease

CONVENIENT AT HOME DOSING
3 times a week or less in under 15 minutes

AIMS TO STOP PROGRESSION OF DISEASE
or prevent disease and improve quality of life

QR-010: RNA target comes with advantages



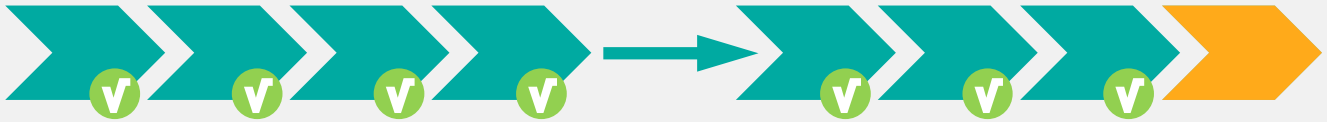
- Single agent
- Low treatment burden
- No predicted drug-drug interactions
- No predicted carcinogenicity
- No predicted teratogenicity

QR-010 for F508del cystic fibrosis

- Patients are ill because of absence of CFTR function. QR-010 has shown to restore CFTR function
- QR-010 has been found safe and well tolerated in ongoing clinical trials
- Smart development program to reduce development time to approval
- Inhalation delivers effectively to lung and distributes to other organs
- QR-010 restores CFTR function in CF patients

Bringing QR-010 to CF patients
Two Clinical Trials by mid-2017

PHASE 1b - PQ-010-001 Safety, Tolerability, Uptake

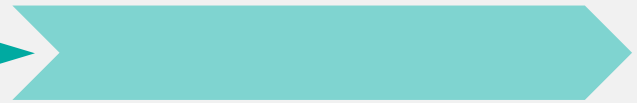


- Safety and tolerability to date
- Demonstration of uptake into blood stream following inhalation after one dose
- Exploratory efficacy data at end of study

NPD - PQ-010-002 Proven ability to restore CFTR function

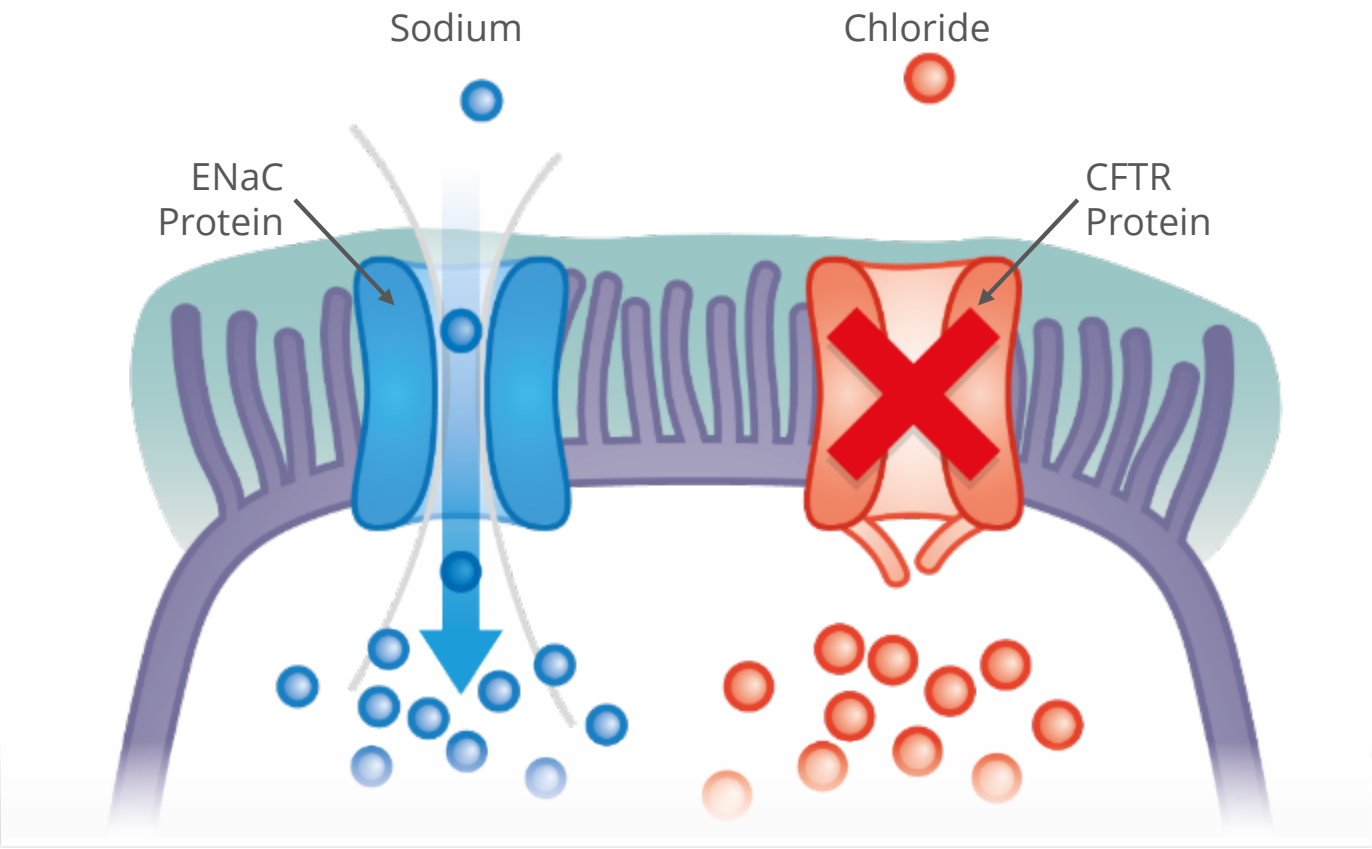
Nasal potential difference biomarker study

Study -003



To begin 2018

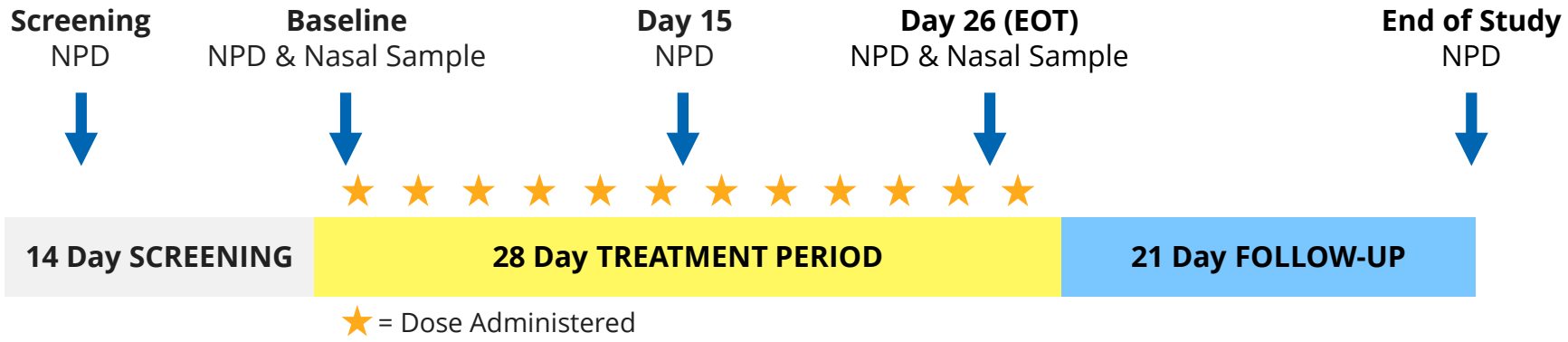
Nasal Potential Difference: Direct measurement of CFTR function



- NPD is the only direct in vivo measurement capable of separating sodium and chloride transport
- NPD has been used as an important endpoint in clinical trials evaluating therapeutic agents

PQ-010-002 Study Design

Open-label NPD study in F508del CF subjects

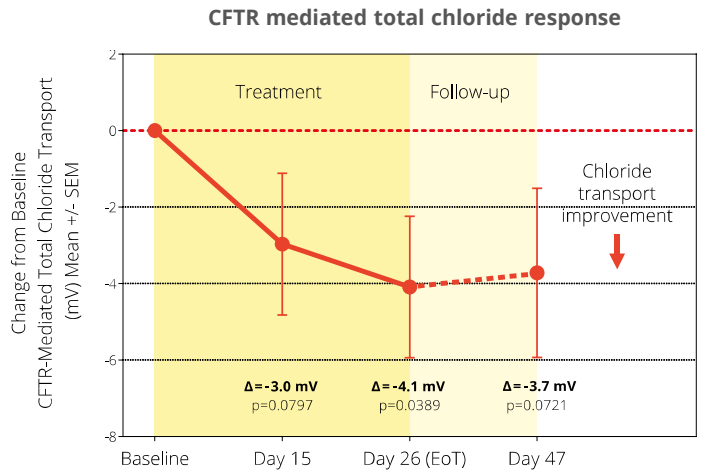


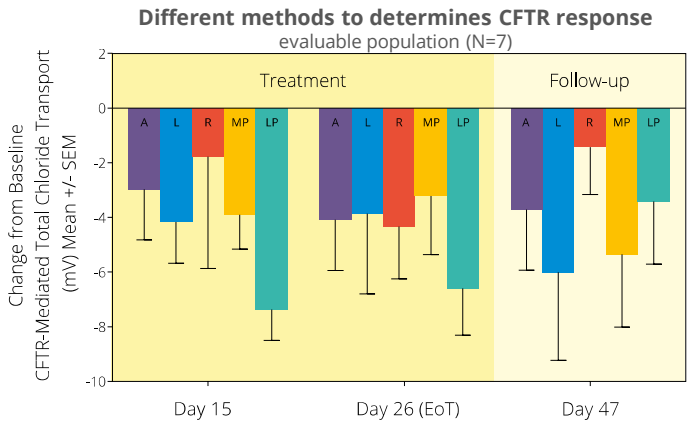
- 8 homozygous and 8 compound heterozygous (all-comers) subjects >18 years old
- Multiple dose design: 12 doses (3 per week x 4 weeks)
- Intranasal administration
- 5 expert participating sites in EU (CTN) and US (TDN)

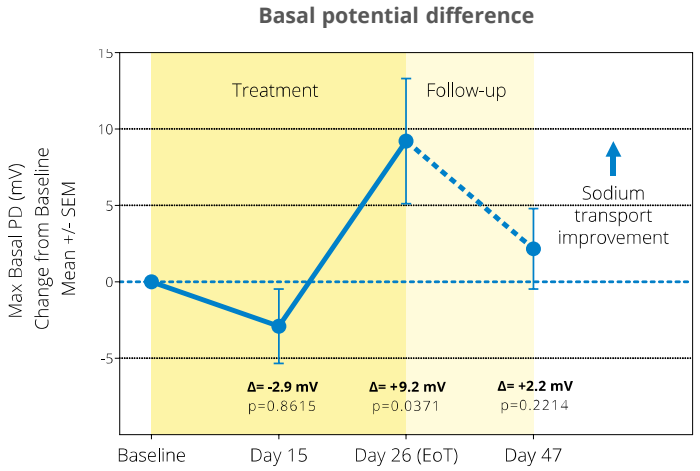
- Endpoints:
  - CFTR-mediated total chloride transport (primary)
  - Other NPD parameters
  - Safety, SNOT-22 and NERS assessments
  - Sweat test (Day 1, 15, 26, 47)

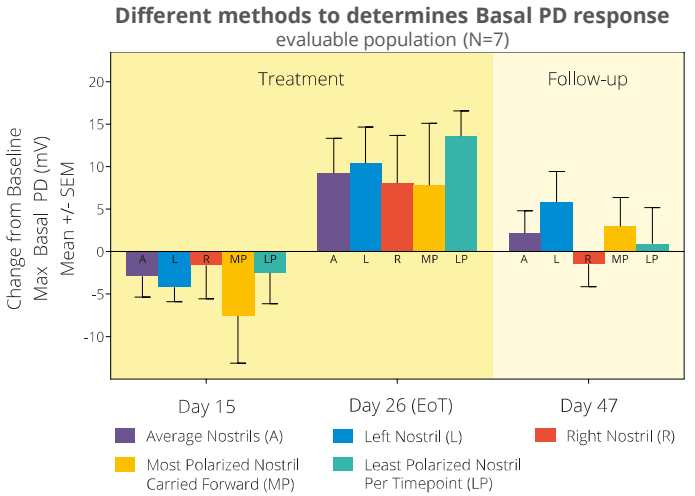
QR-010 restores CFTR function

Results of "NPD" Study





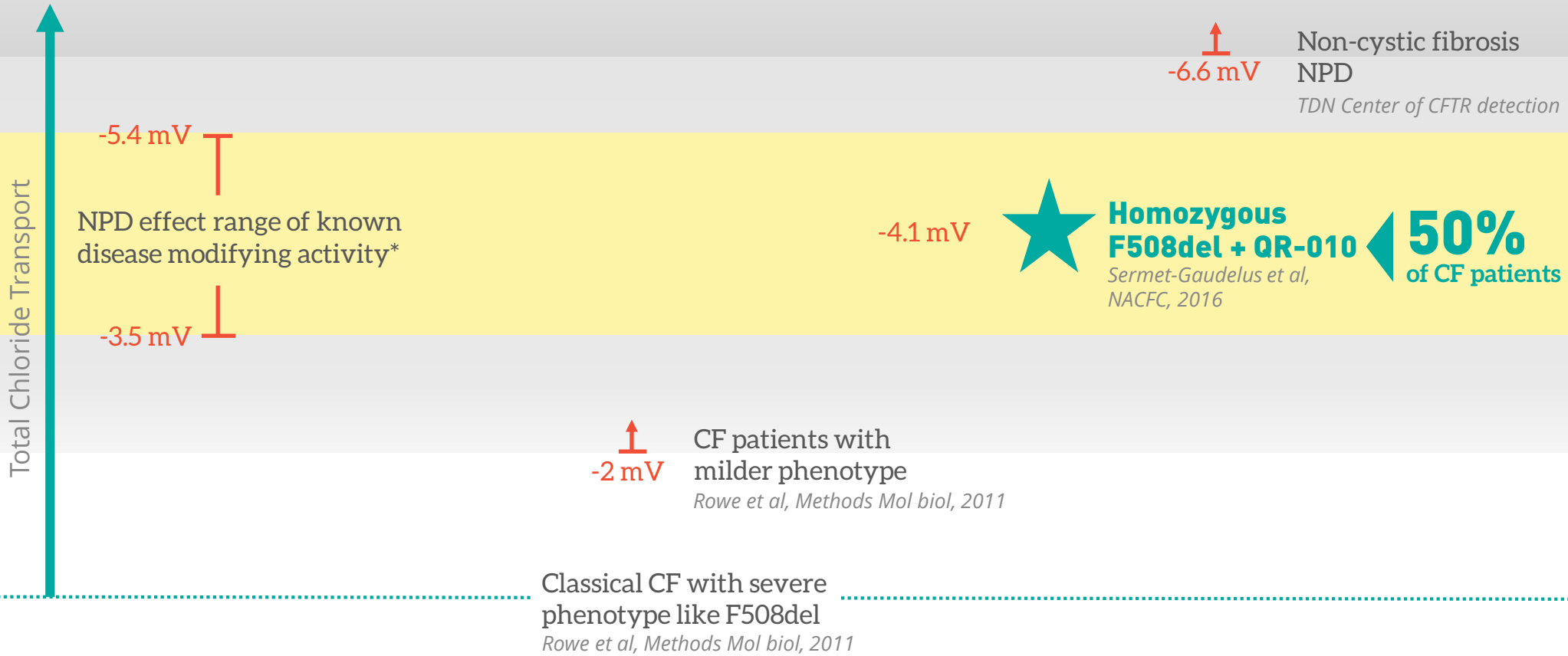




Key takeaways:

- Strong response in CFTR mediated chloride transport
- Statistically significant response per-protocol subjects
- Durable response 21 days post treatment
- All secondary measurements are supporting restoration of CFTR function
- Irrespective of the chosen method of analysis an improvement is observed
- Max Basal PD is direct measurement of ENaC activity as measured by sodium transport
- Basal PD confirms functional data for CFTR activity
- All secondary measurements are supporting restoration of sodium transport
- Irrespective of the chosen method of analysis an improvement is observed

QR-010: CFTR levels that are expected to be disease modifying

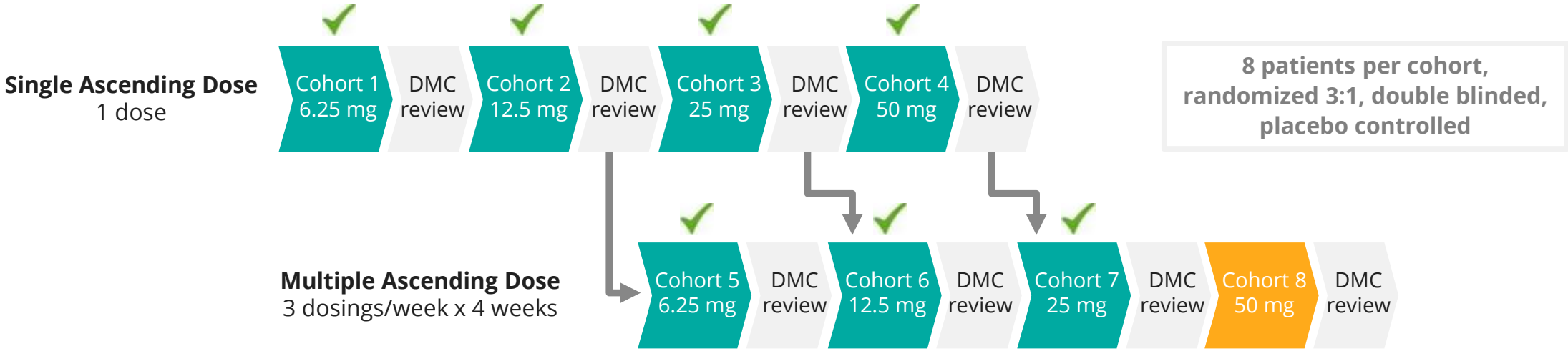


Interpretations are adapted from publications

* Based on responses in ivacaftor studies in G551D

Phase 1b Safety and Tolerability Study

Top line data expected to be announced in September 2017

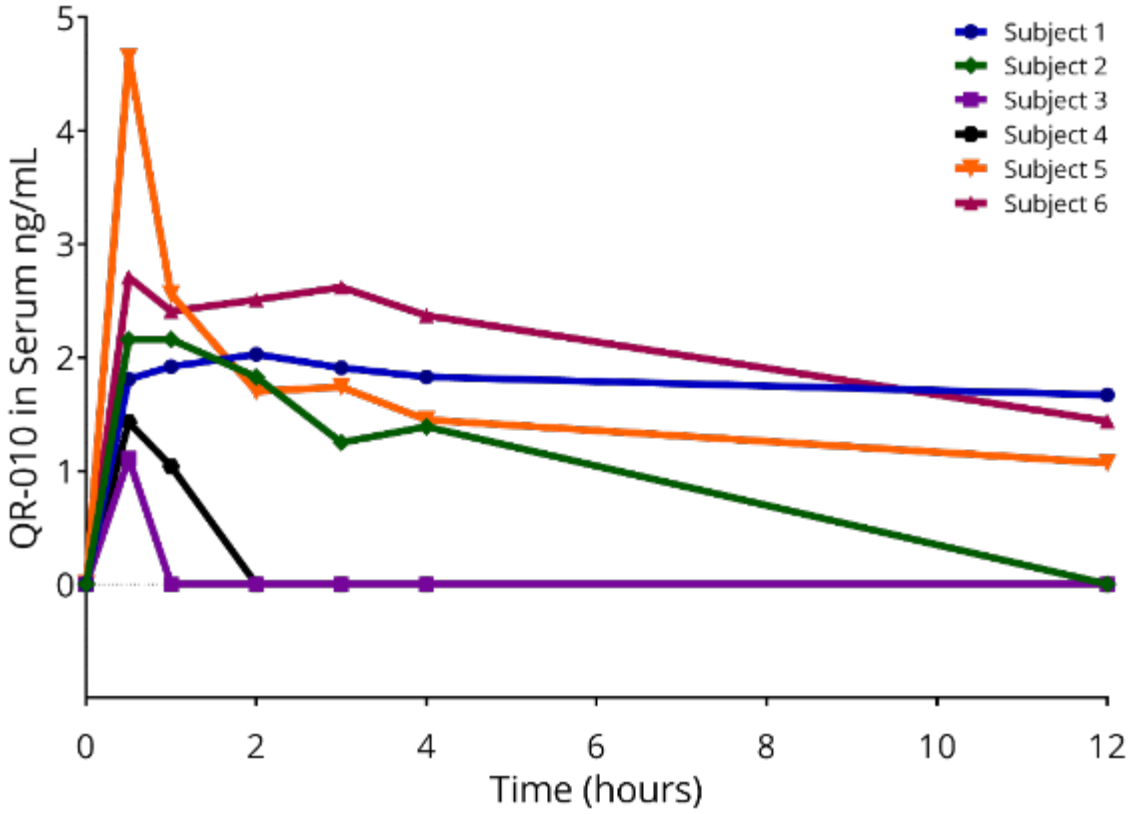


- 64 homozygous F508del CF patients (>18yrs)
- Inhalation through Pari eFlow nebulizer
- Participating investigators: 27 sites EU (CTN) and North America (TDN)
- All 4 SAD cohorts and three MAD cohort have been completed and reviewed by the DSMC
- MAD Cohort 7: All subjects completed dosing

- Endpoints:
  - Safety, tolerability, and pharmacokinetics
  - Exploratory efficacy
    - FEV_1
    - CFQ-R Respiratory Symptom Score
    - Weight gain
    - Sweat chloride)

QR-010 is measurable in serum following single dose administration

Concentrations of QR-010 Measured in Serum Following a 50 mg Dose



- Single Dose Cohorts Confirm QR-010 is absorbed following inhalation
- Single dose safe and well tolerated
- 25 and 50 mg with detectable QR-010 in serum

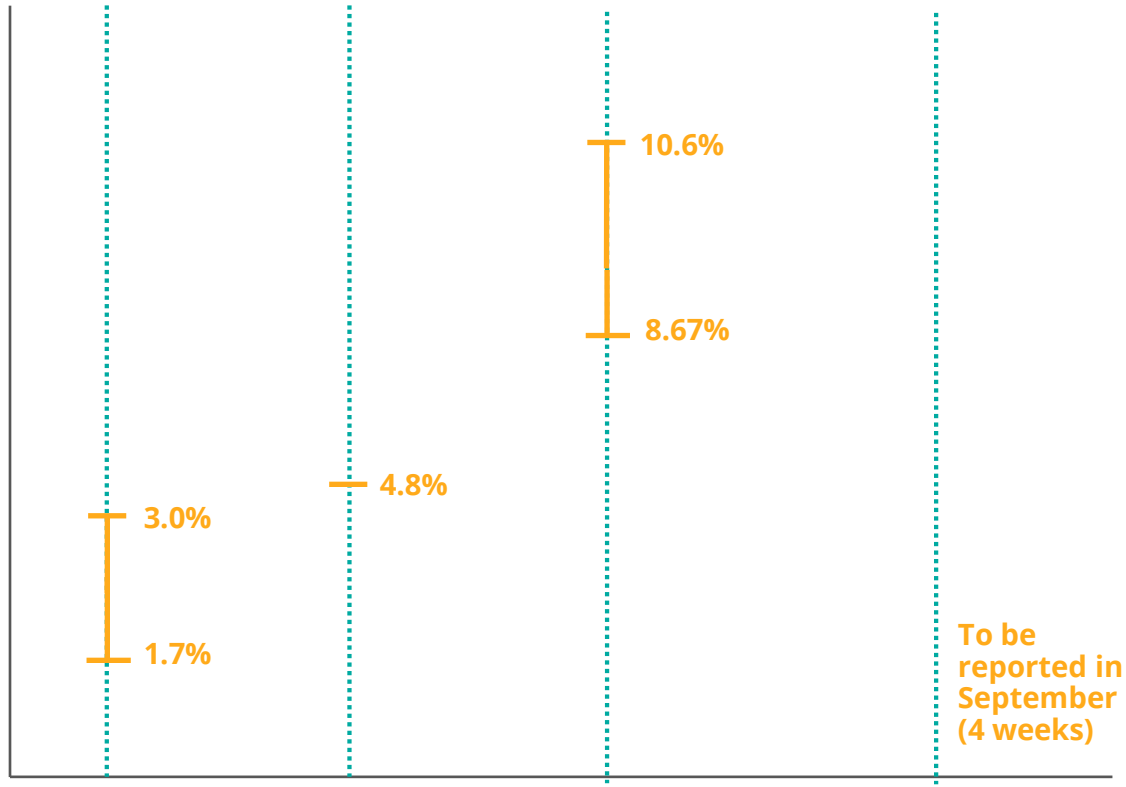
Phase 1b:

Exploratory efficacy endpoints

Efficacy Outcome	Description	Type	Strength	Weakness
FEV1	Measures airflow	Surrogate	• Well standardized • Lung specific • Repeatable/Reliable	• Variation • Effort dependent • Influenced by con meds • Less sensitive in well subjects
CFQ-R RSS	Disease specific patient reported outcome measured	Clinical outcome	• Well standardized • Useful over most ages • Translated widely	• 2 week recall period • Learning effect
Weight	Increases in weight improves overall health in CF	Biomarker	• Objective sign of health • Easy to assess	• Long term only • Influenced by other factors
Sweat Chloride	Indirect measure of CFTR function	Biomarker	• Well accepted • Performed by all CF centers	• Oligos may not get to glands
Nasal Potential Difference	Direct measure of CFTR function	Biomarker	• Well accepted	• Technically hard • Few reliable centers

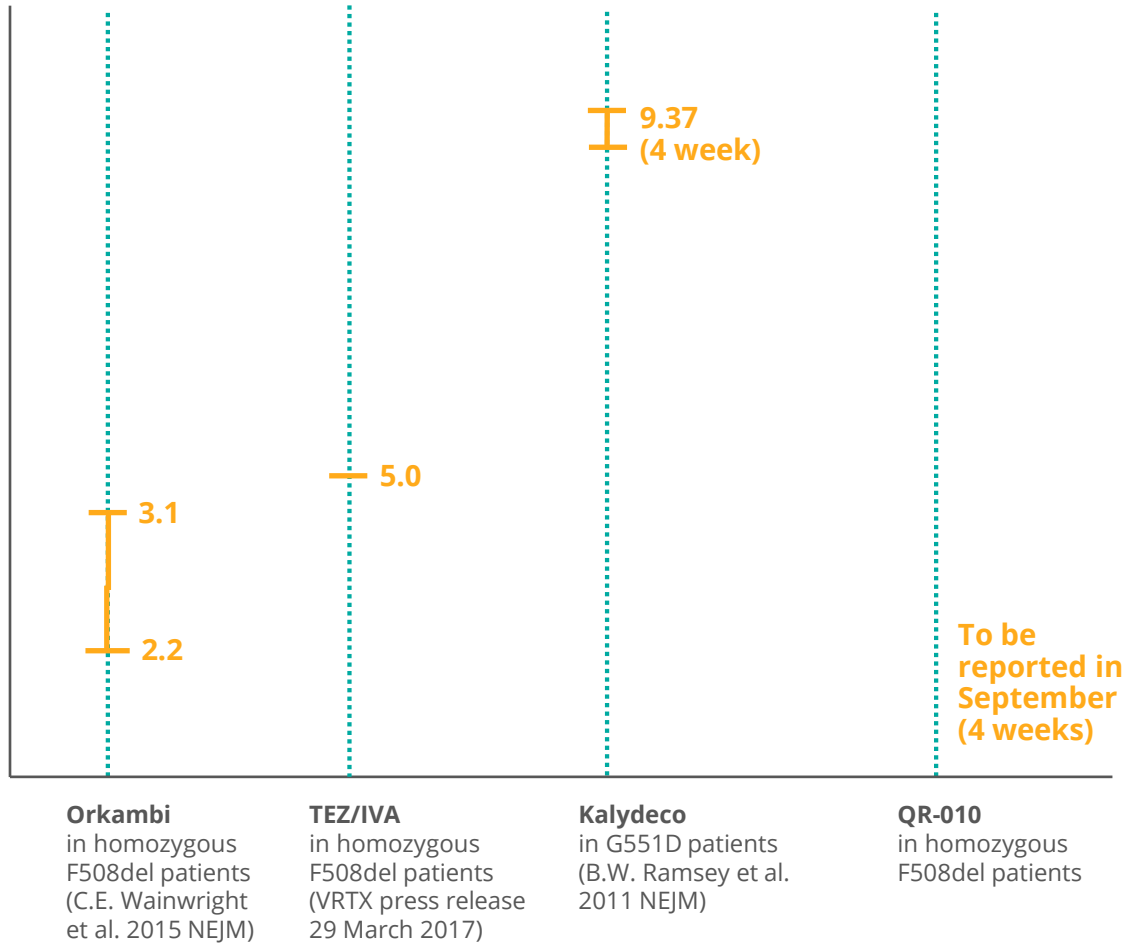
Exploratory efficacy: Absolute Change in FEV_1

- **Description**
  Measures airflow
- **Type**
  Surrogate endpoint
- **Strength**
  - Accepted by Regulatory Agencies
  - Easy to perform; well standardized Historical/registry data from other drugs in CF and other diseases
  - Lung specific Repeatable/Reliable
- **Weakness**
  - Diurnal variation
  - Influenced by con meds
  - Ceiling effect for improvement
  - Reflect large airways health so can be
  - insensitive in early stage disease
  - Safety vs efficacy measurement? Serial assessment in our trial



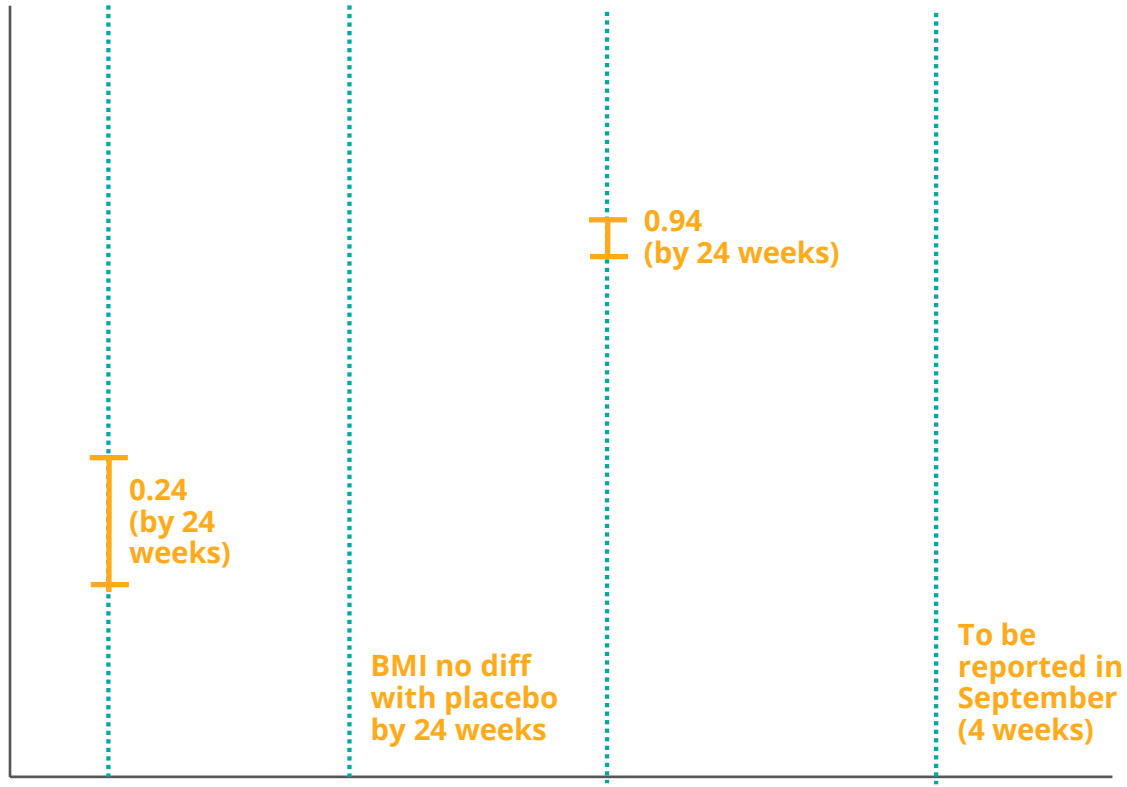
Exploratory efficacy: CFQ-R RSS

- **Description**
  Disease specific patient reported outcome measured
- **Type**
  Clinical outcome
- **Strength**
  - Used in most CF trials as PRO
  - Independent measure from FEV1
  - Well standardized
  - Useful over most ages
  - Translated widely
- **Weakness**
  - Significance poorly understood
  - Potential for recall bias



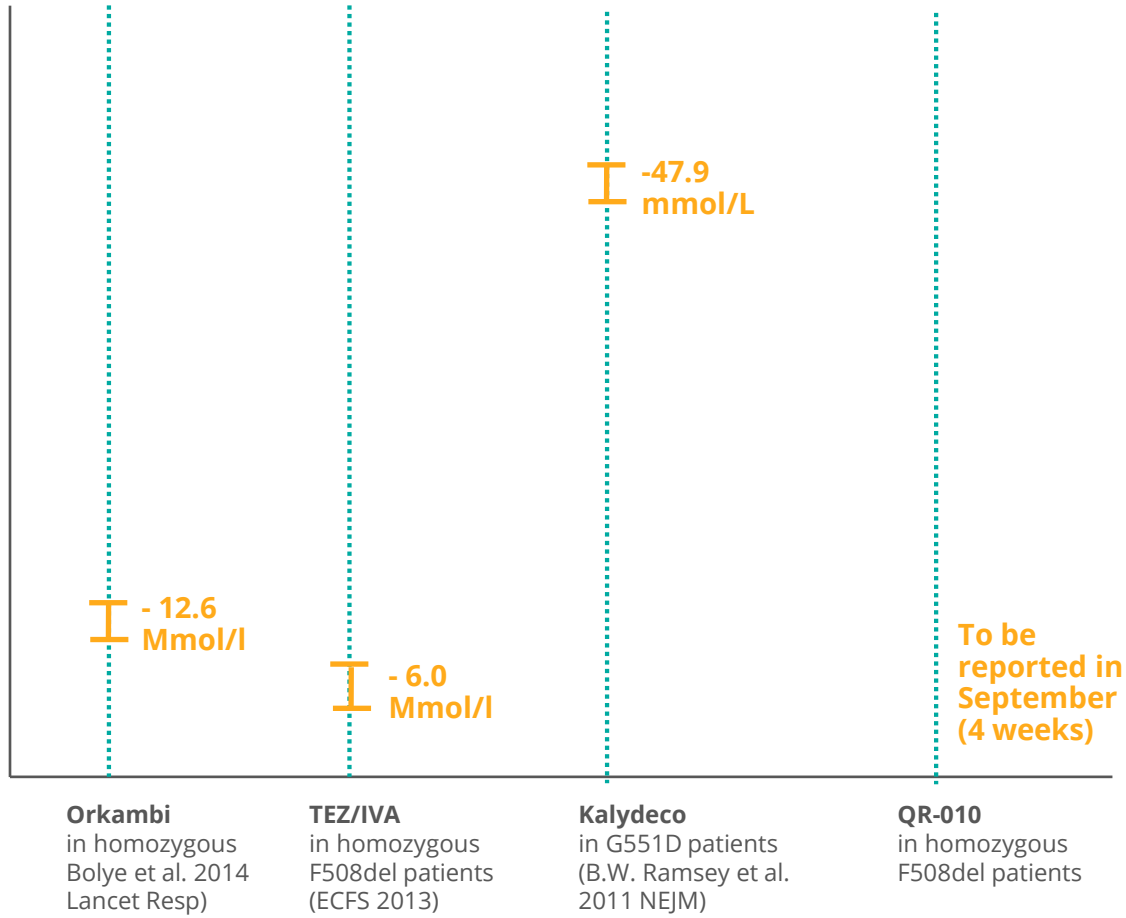
Exploratory efficacy: BMI (Weight)

- **Description**
  Increases in weight improves overall health in CF
- **Type**
  biomarker
- **Strength**
  - Objective sign of health other than lung function
  - Easy to assess
- **Weakness**
  - Long term only
  - Influenced by other factors (indirect drug effect)



Exploratory efficacy: Sweat Chloride

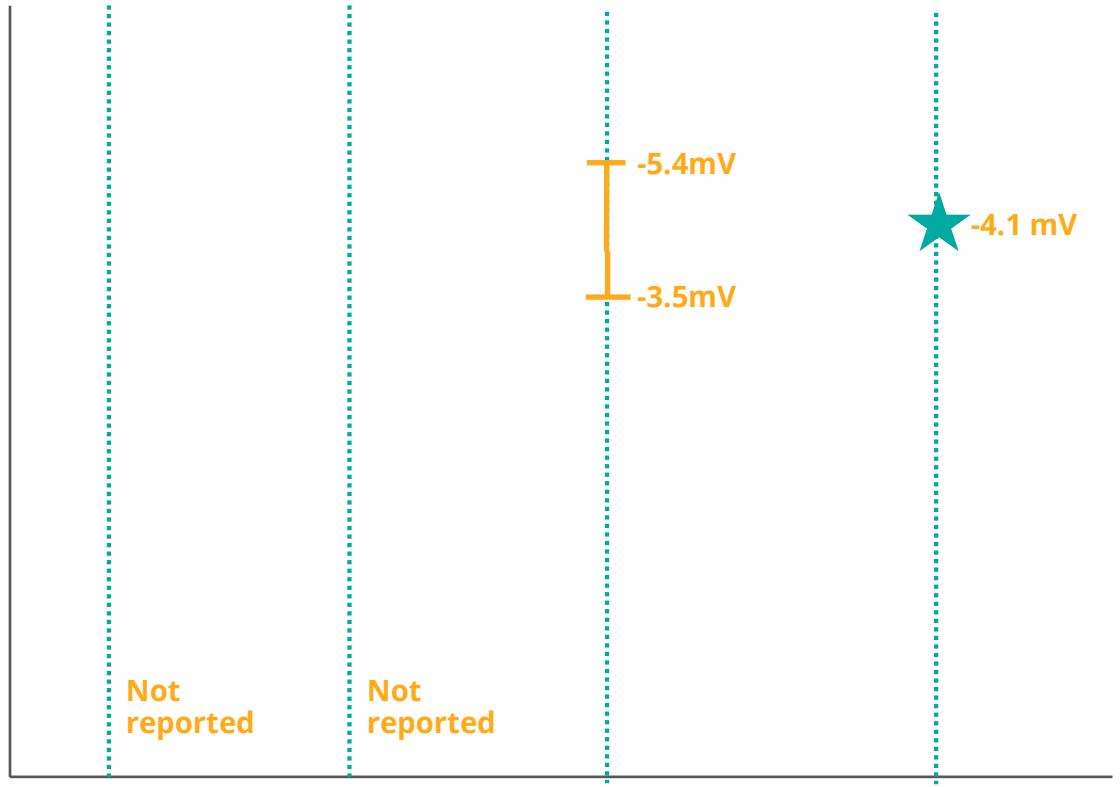
- **Description**
  Indirect measure of CFTR function– high Cl- diagnostic for CF
- **Type**
  biomarker
- **Strength**
  - Well accepted dx tool
  - Non invasive and performed by all CF centers
- **Weakness**
  - Oligos may not get to glands
  - No direct correlation with clinical response



Nasal potential difference

- **Description**
  Direct measure of CFTR function in relevant tissue
- **Type**
  biomarker
- **Strength**
  - Well accepted
- **Weakness**
  - Technically hard
  - Few reliable centers

QR-010 restores CFTR function in subjects homozygous for F508del



QR-010 Innovation to treat F508del CF

- Innovative RNA approach as single agent therapy
- Safe and well tolerated to date
- Systemic uptake detected after single dose
- Restoration of CFTR activity observed in NPD biomarker trial in homozygous F508del patients

Nasal Potential Difference:
Advances in Methods for Clinical Trials

Steven M. Rowe, MD MSPH

UAB Center for CFTR Detection (CCD)

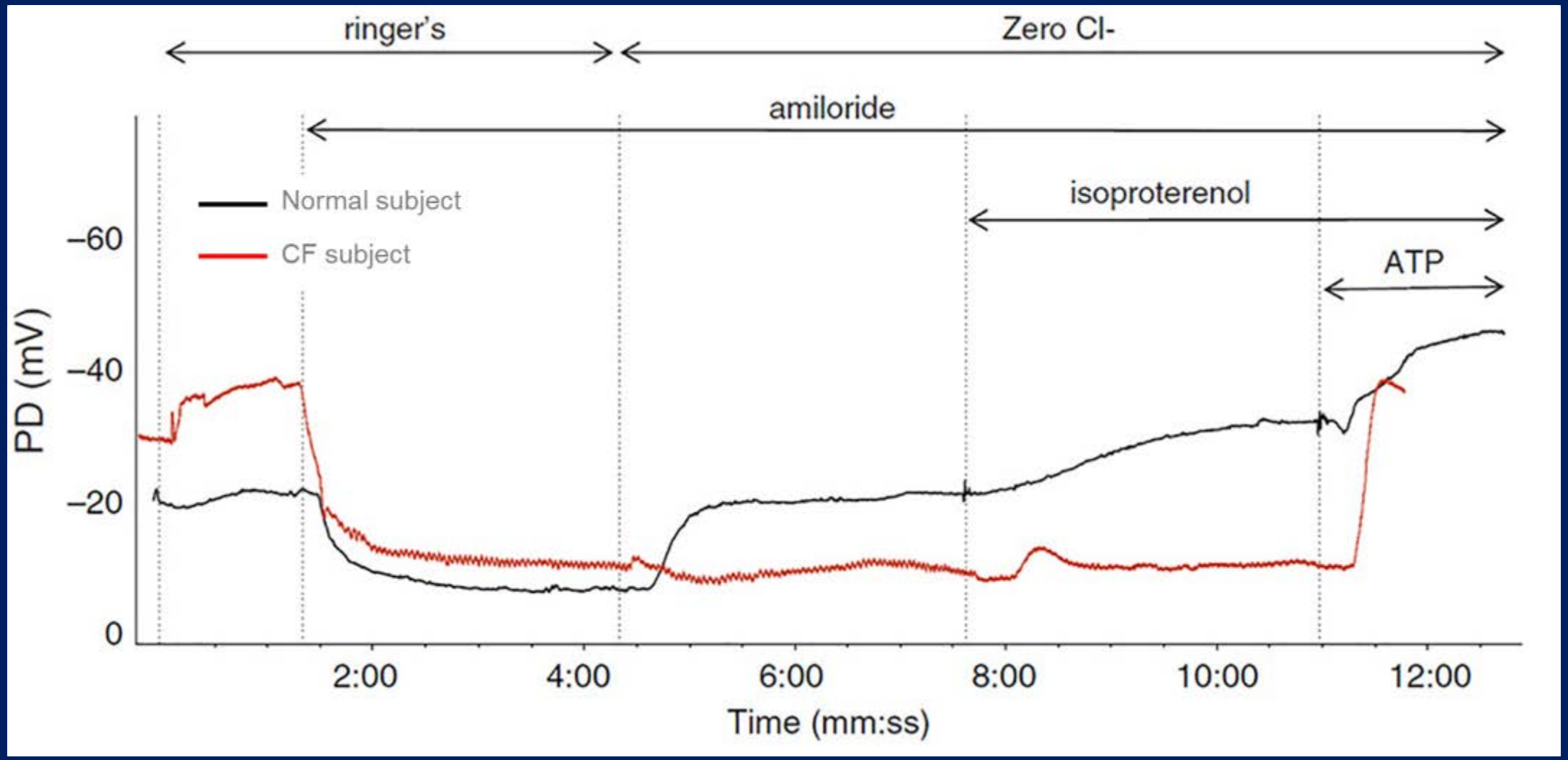
CF-Therapeutics Development Network

Funded by CFF and NIH

History of Nasal Potential Difference (NPD)

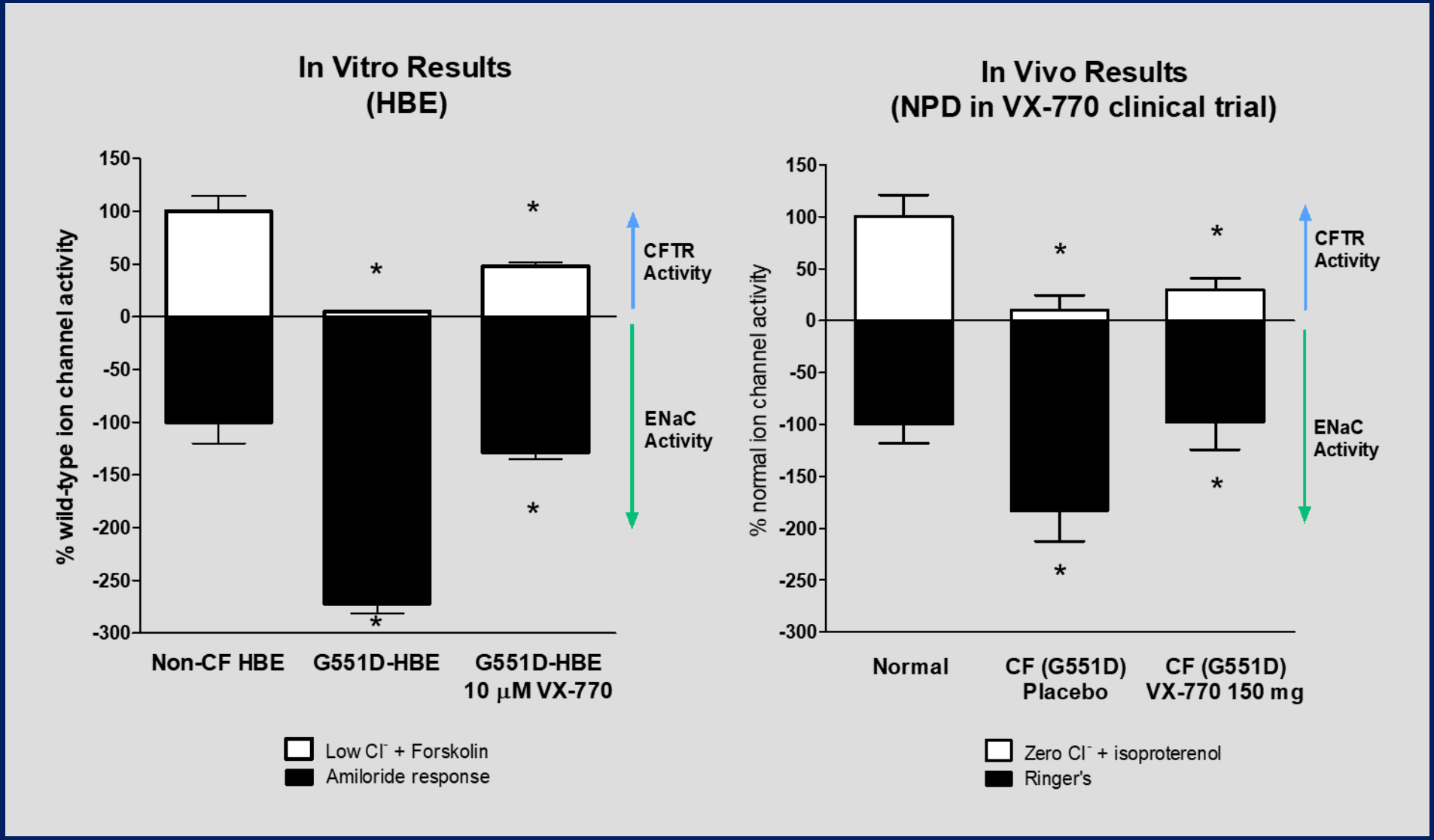
- NPD was originally described as test to diagnose CF – effectively separating healthy individuals who had functional CFTR protein from individuals with CF
- Unlike sweat chloride, NPD is a direct measure of CFTR function, measuring chloride transport in the respiratory epithelium
- It can also simultaneously measure activity of the sodium channel ENaC, which also regulates ASL depth and mucus clearance
- NPD has been used in clinical trials as a direct measure of CFTR function, but has generally predicted results with subsequent clinical testing

Nasal Potential Difference



Rowe et al. Methods Mol Bio 2011

Relationship Between In Vitro and In Vivo Results with Ivacaftor: NPD

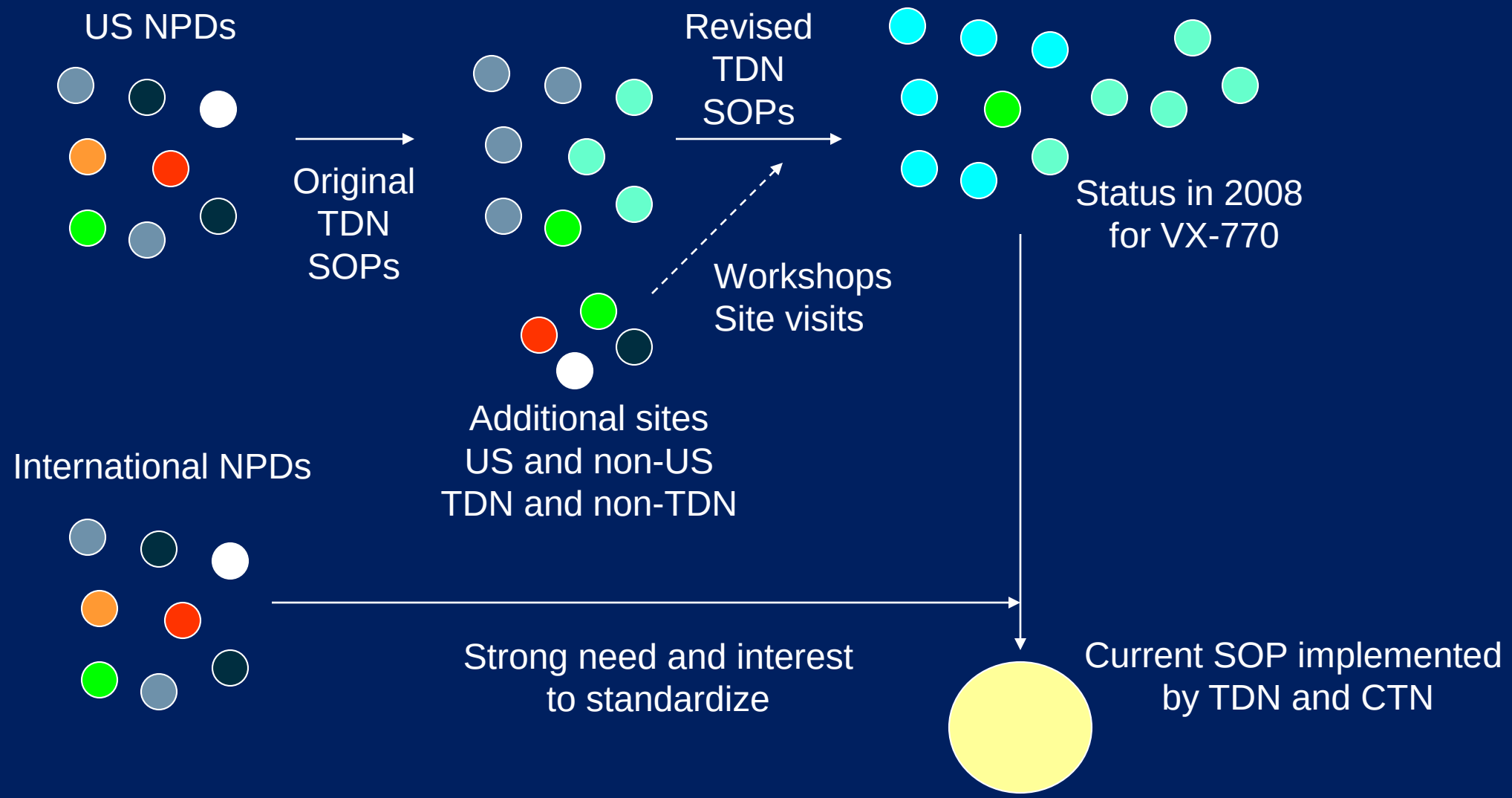


Rowe SM, ECFS 2010

History of Nasal Potential Difference (NPD)

- One of the major challenges for the outcome measure is that requires operator skill, and there were significant variations in the technique and equipment used
- To address this in an era of CF clinical testing, the Center for CFTR Detection has worked over many years to standardize NPD for use in clinical trials
- After several iterations of improvement, standardization is now agreed upon by approved NPD centers in US and Europe
- Techniques substantially improved sensitivity, within subject reproducibility, and ability to incorporate in rigorously designed clinical trials

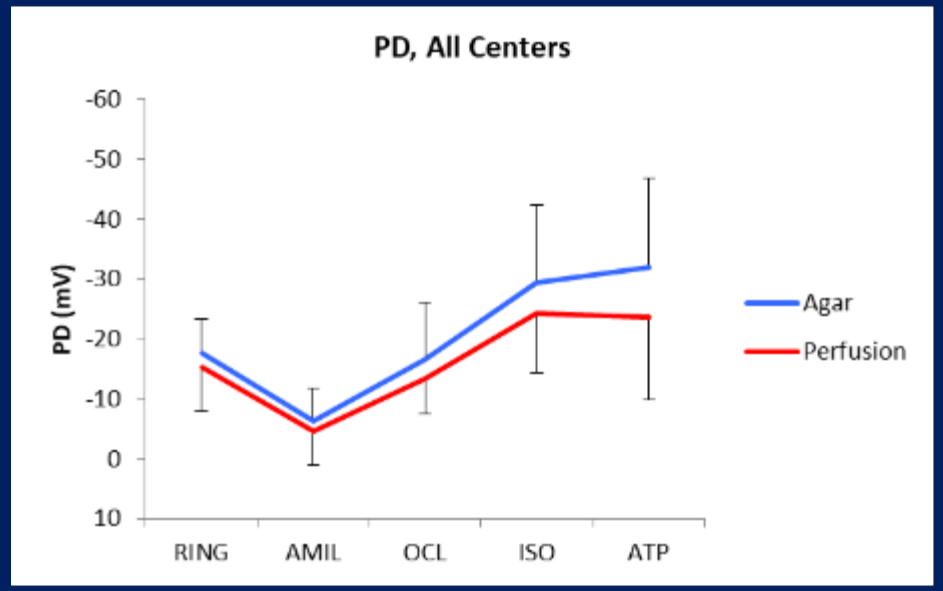
NPDs Standardization Effort

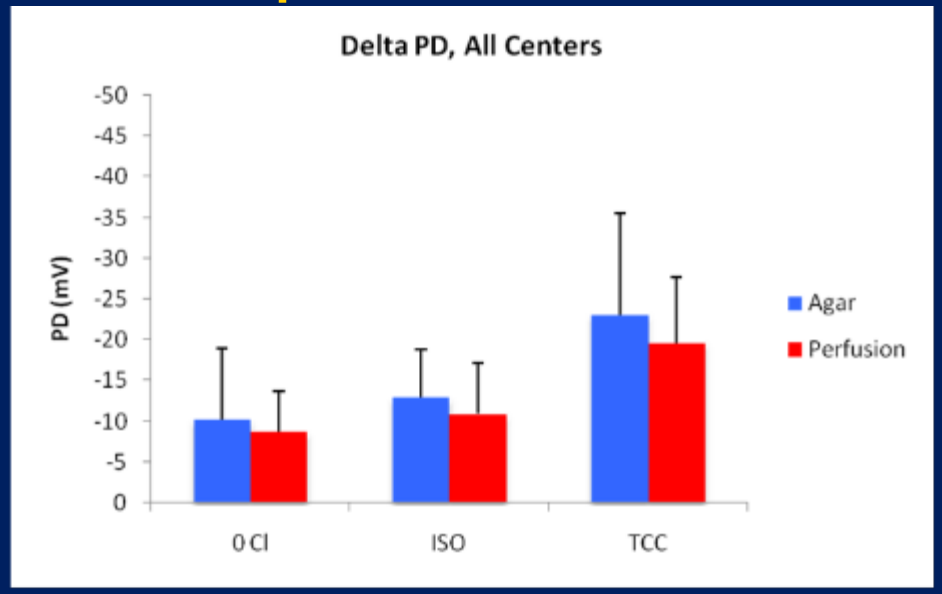


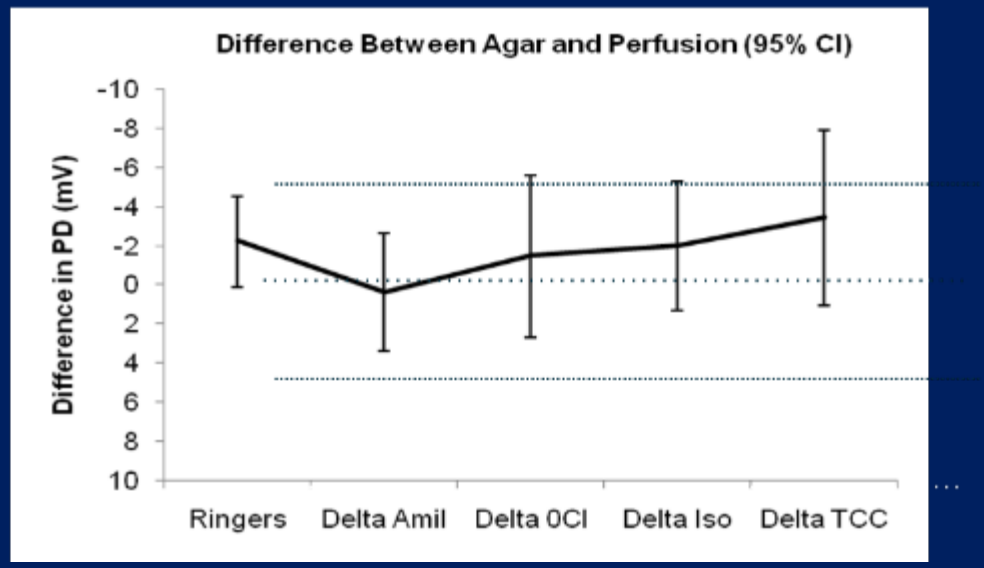
Key Improvements to NPD

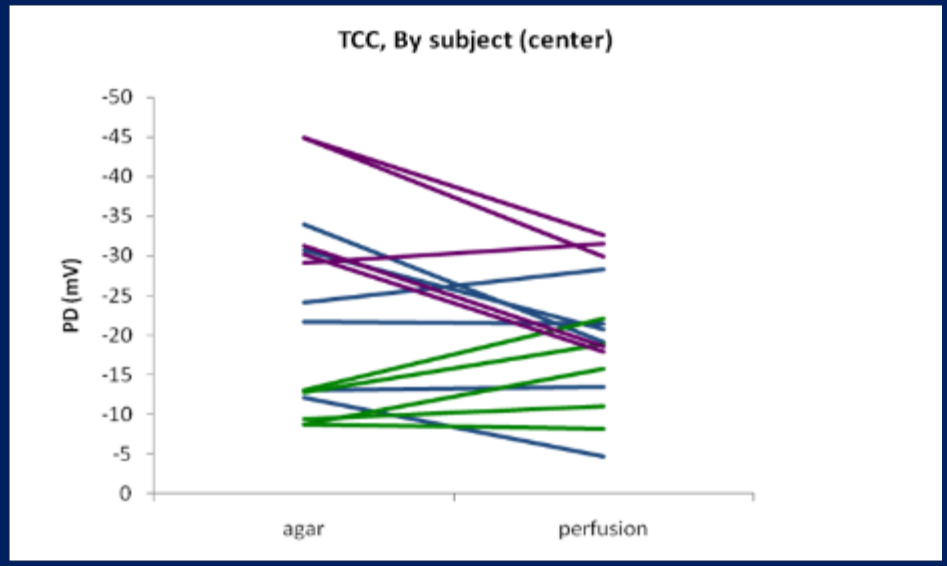
- Centralized blinded reading
- Standardized operating procedure
- Central sourced kits
- Electronic data capture
- Consistency across multiple study centers
- This procedure has been adopted for all NPD studies since 2009, (and 2012 in Europe) improving interpretability of trial results

Potential Difference Method Improvement



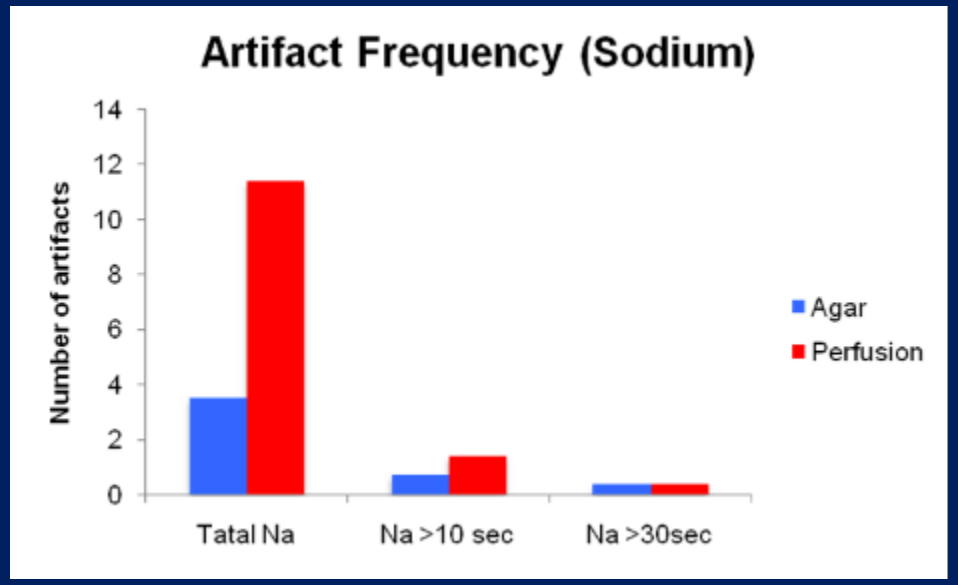


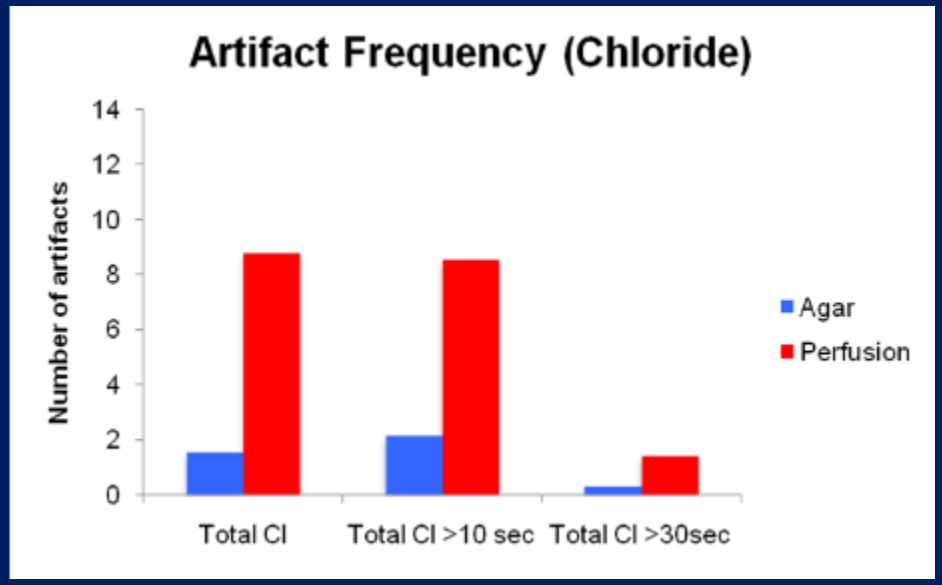




Solomon et al., *Chest* 2010; 138(4):919-28

Important Reductions in Artifact Frequency





- Reduced artifact frequency with non-perfusion compared to perfusion approach

- Observed in sodium and chloride measures

Solomon et al., *Chest* 2010; 138(4):919-28

Intraclass Correlation Amongst 5 NPD Scorers indicates Robust Correlation of Key Quantitative

Intraclass Correlation of Qualitative Scores Amongst 5 NPD Scorers		
	ICC	P-Value
Ringer's	0.985	<0.005
$\Delta_{Amiloride}$	0.965	<0.005
TCC	0.995	<0.005
TCC, Total Chloride Conductance ($\Delta_{0\ Cl- + Isoproterenol}$)		

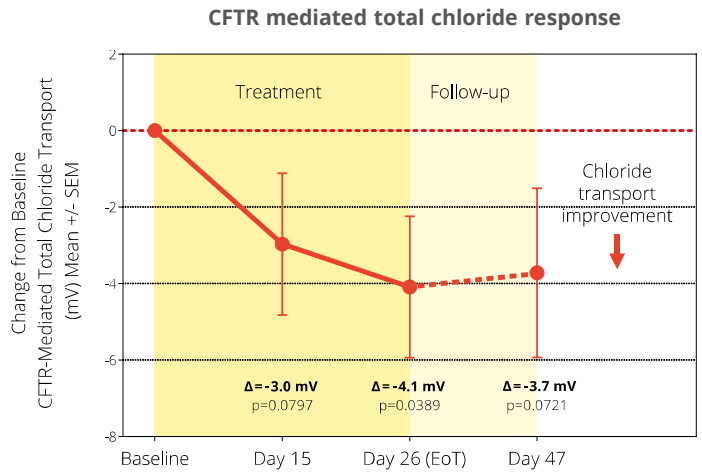
Solomon et al., *JCF* 2017

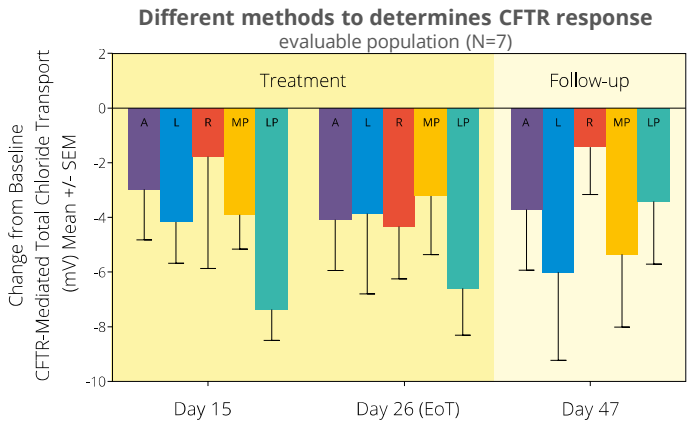
Implementation in ProQR-002

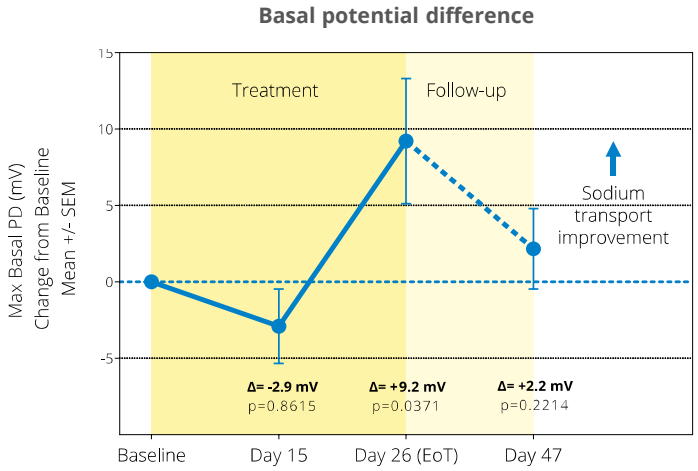
- Provided key opportunity to confirm mechanism of action for first in class oligimer
- Incorporated blinded, batched analysis via electronic data capture with strict a prior criteria
- High rate of interpretable tracings (94%)
- Concordance of chloride and sodium transport data provide confidence in overall findings
- Sensitivity analysis also supportive

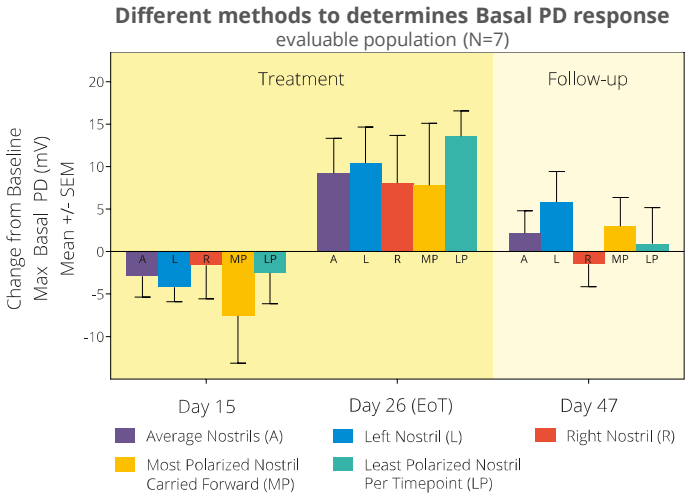
QR-010 restores CFTR function

Results of "NPD" Study









Key takeaways:

- Strong response in CFTR mediated chloride transport
- Statistically significant response per-protocol subjects
- Durable response 21 days post treatment
- All secondary measurements are supporting restoration of CFTR function
- Irrespective of the chosen method of analysis an improvement is observed
- Max Basal PD is direct measurement of ENaC activity as measured by sodium transport
- Basal PD confirms functional data for CFTR activity
- All secondary measurements are supporting restoration of sodium transport
- Irrespective of the chosen method of analysis an improvement is observed

Significance of ProQR-002 Results

- While this was a nasal POC study, results affirm the hypothesis that QR-010 can restore CFTR function to F508del CFTR
- NPD has successfully predicted efficacy in subsequent studies; improved chloride and sodium transport is particularly meaningful
- There remains significant unmet need for the treatment of CF patients with one or two copies of F508del

Inherited Retinal Dystrophies

A major opportunity for RNA-based therapeutics

Presenter: Peter Adamson

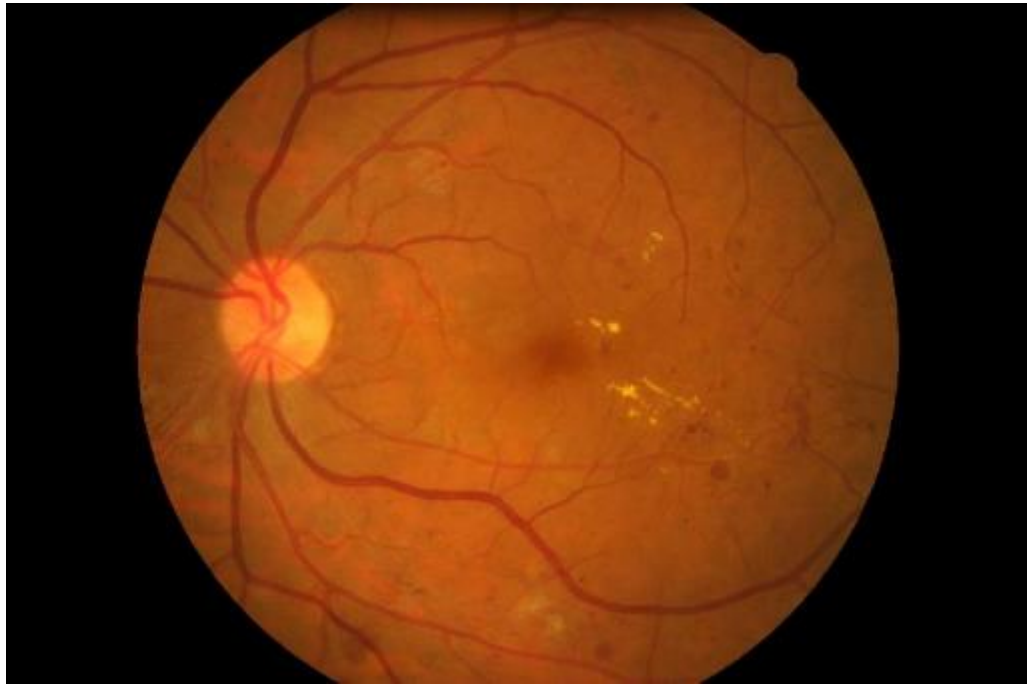
Inherited Retinal Dystrophies

The Opportunity

A wide array of mutations within a variety of genes, encoded within both intronic and exonic regions, yields a significant opportunity to perform “corrective” RNA editing in IRDs.

There are consequently many thousands of molecular target mutations within 100s of genes associated with IRD.

Such genes can be in any retinal cell-types.



RNA editing in Inherited Retinal Dystrophies

Specificity of RNA approach and advantages of intravitreal delivery

- **A wide-array of RNA defects can be altered**
  Specific mutations, can be specifically targeted with a variety of approaches
- **RNA editing allows normal level of gene-expression**
  No toxic effects of supra-high expression of transgenes
- **Specific and selective pharmacology**
  20 and 21 mers show almost no off-target effects
- **2'Ome/PS-modifications allows efficient entry to cells,**
  Particularly in the eye following IVT injection
- **2Ome-PS oligonucleotides display long retinal PK (months) vs vitreal PK (days)**
  Allows for infrequent IVT dosing
- **Low Systemic exposure**

Ophthalmology Pipeline

Several undisclosed targets

- ✓ Several interesting targets selected
- • Next step: sequence optimization

QRX-1011
Stargardt's Disease

- ✓ Molecule sequence optimized
- • Next step: chemistry optimization

QRX-504
Fuchs (FECD)

QRX-421
Ex13 Usher Syndrome

QRX-411
PE40 Usher Syndrome

- ✓ Clinical candidate selected
- • Ready to start IND-enabling studies

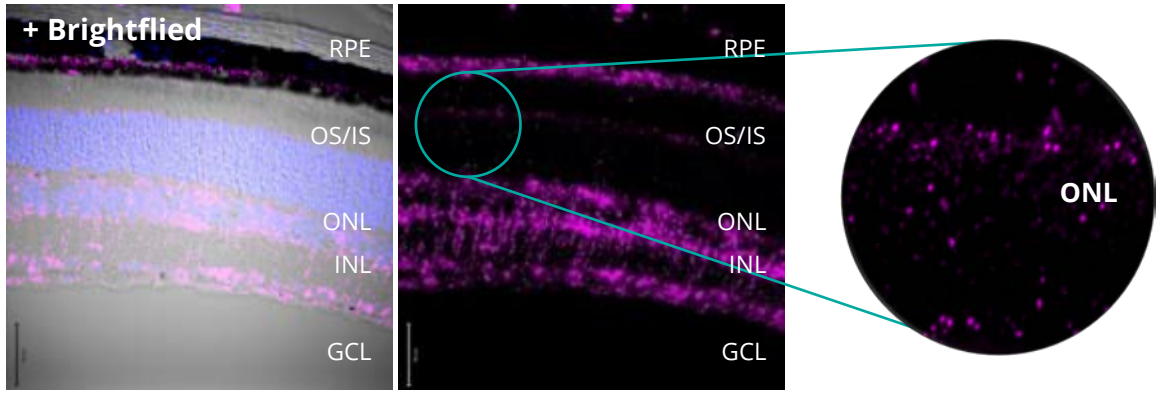
QR-110
LCA10
~2,000 patients

- ✓ IND open
- ✓ CTA Approval (BL)
- ✓ Fast Track Designation

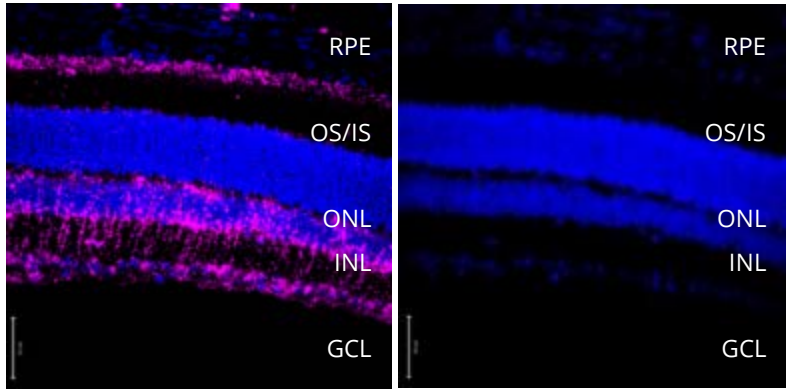
Targeting of oligonucleotides in the retina

Intravitreal oligonucleotides target all cellular layers of the retina

Cy5-QRX-421

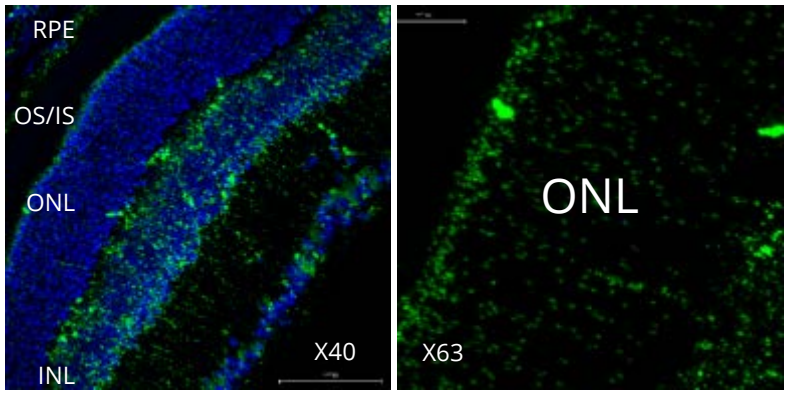


Immediately post IVT dose

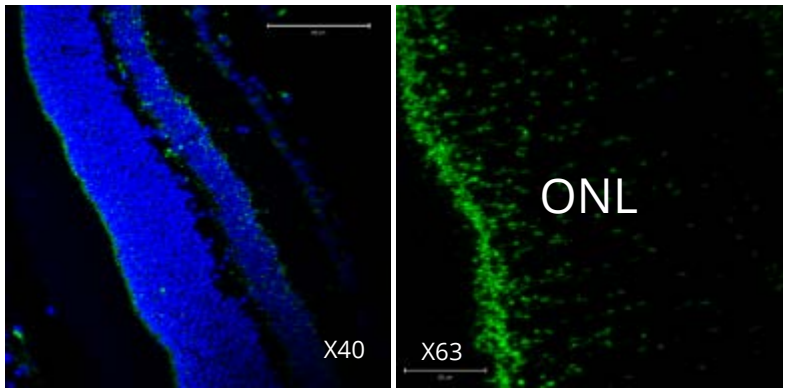


7 days POST IVT dose

FAM-6-QR-110



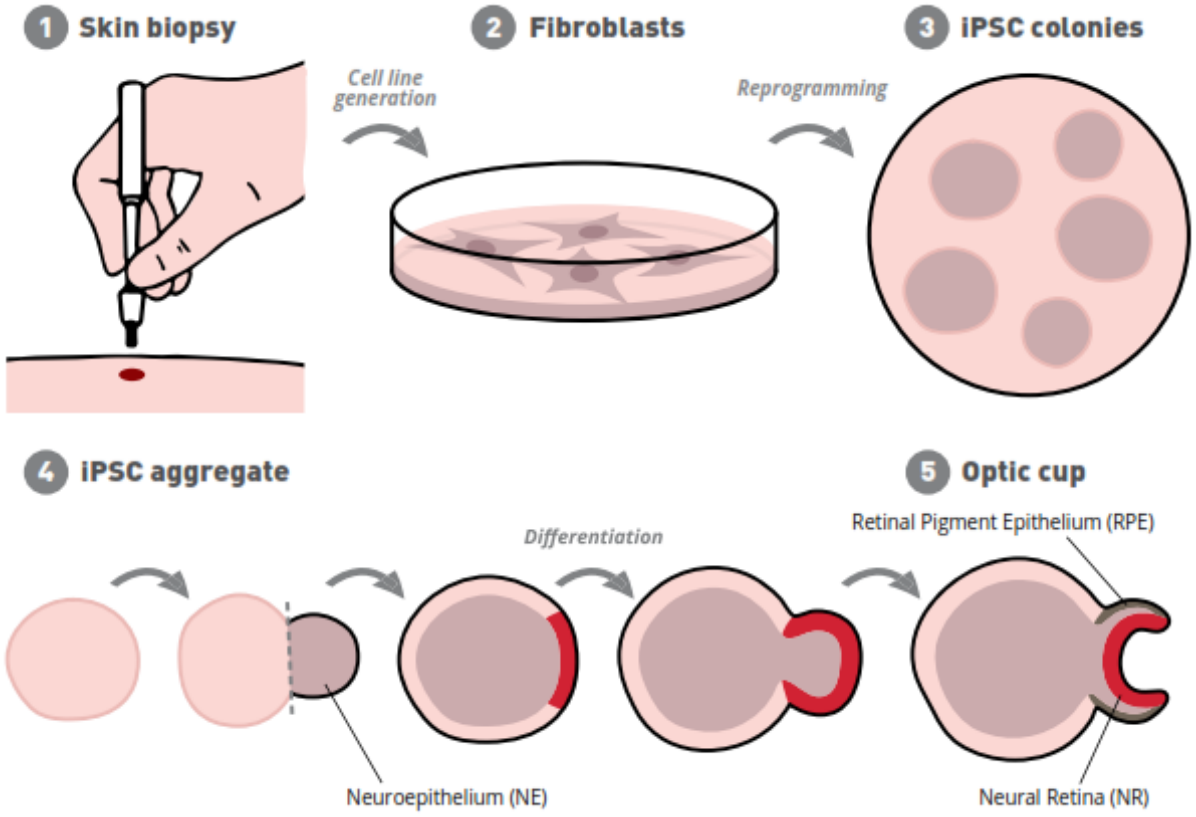
14 days



60 days

Dose 1µl 25 µg/µl in c57/bl6 mice Cy5-QRX-411 DAPI FAM-6-QR-110

Eye cup model forming retinal structure

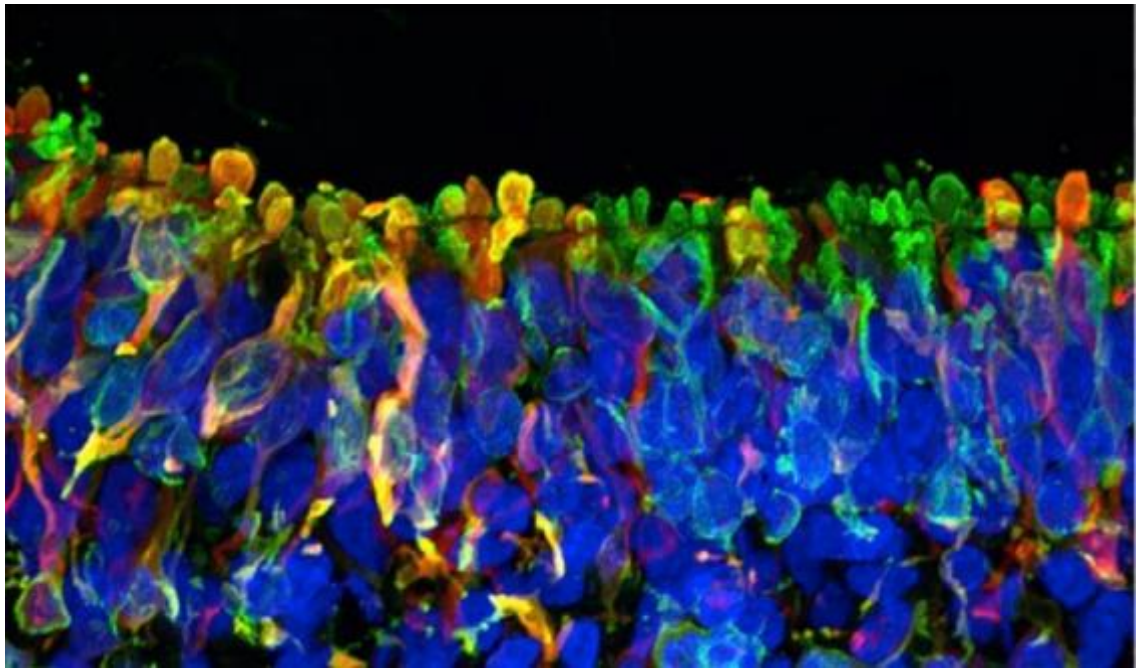


- A real 3D model of human **patient** retina containing all retinal cell layers
- Can be grown from any **patient** with any **IRD**
- Eye-cups have human mutation
- Present and show the effect of the mutation in human cells
- Can test human therapeutic molecule instead of surrogate
- Has been used instead of animal efficacy data in successful regulatory submissions in US and EU

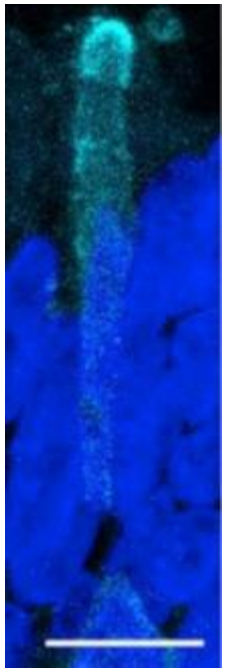
Ramsden et al., 2016

Patient-derived iPSC optic cups

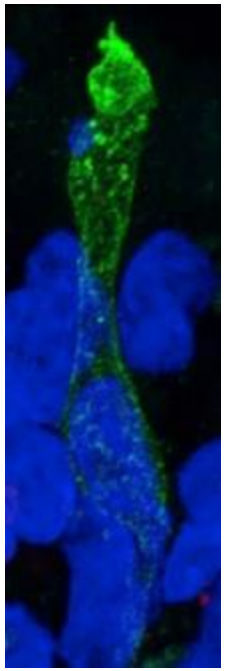
Optic cup is an organoid model containing differentiated photoreceptor cells



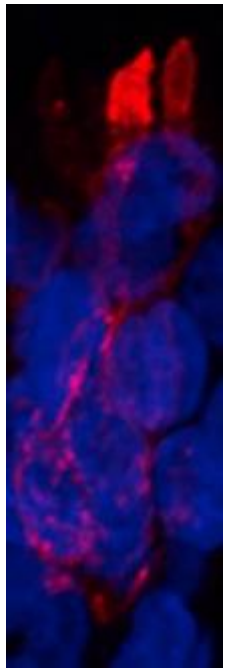
Recoverin cone-arrestin



Detail:
Rhodopsin



Detail:
L/M-opsin



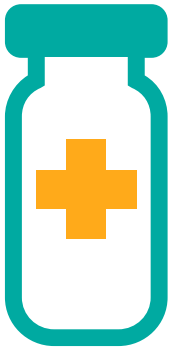
Detail:
S-opsin

Parfitt et al., 2016

QR-110

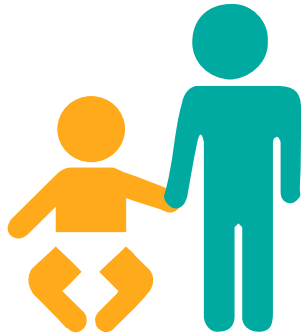
Splice correction for p.Cys998X causing Leber's congenital amaurosis Type 10 (LCA10)

QR-110 for LCA10

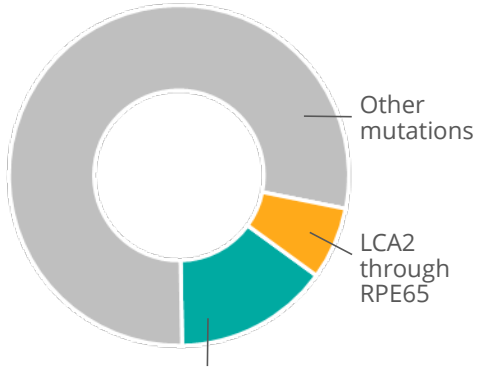


No therapy available

Eye

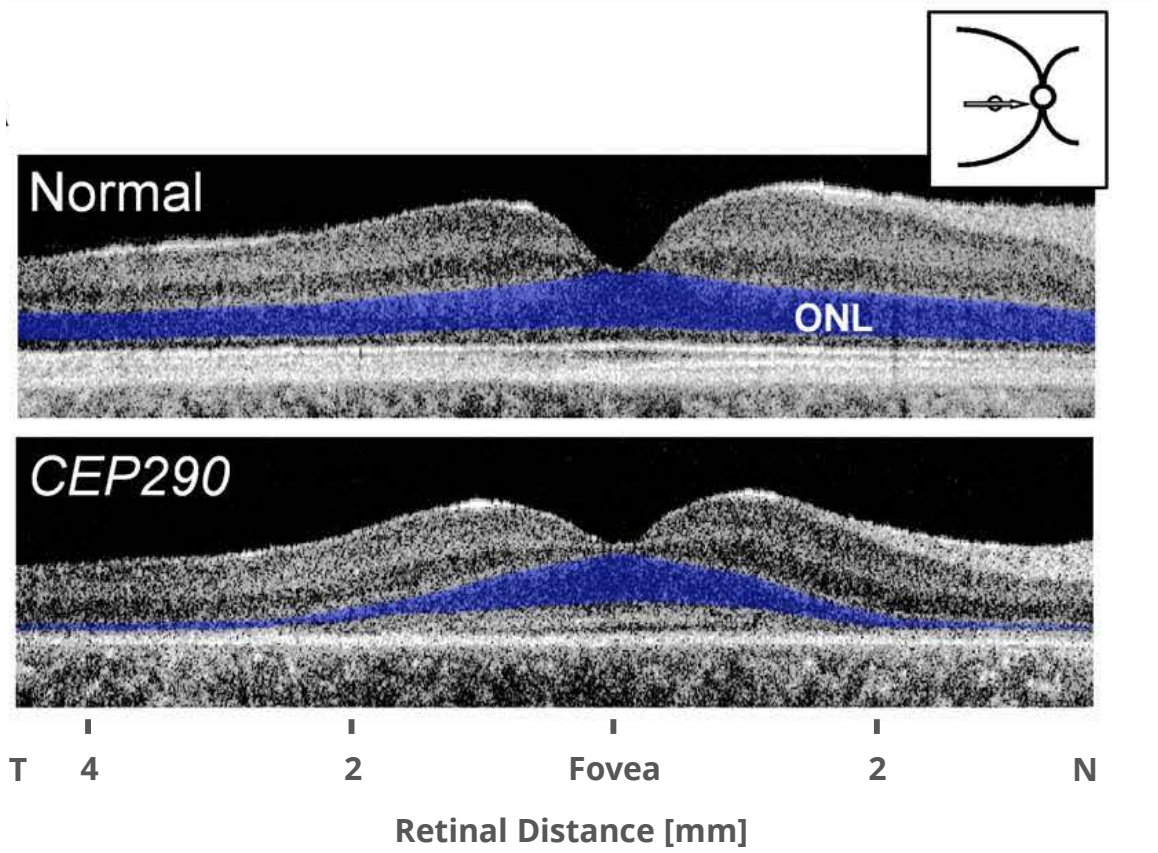


Lose sight in first years of life



~2,000 patients with LCA10 through p.Cys998X in Western world

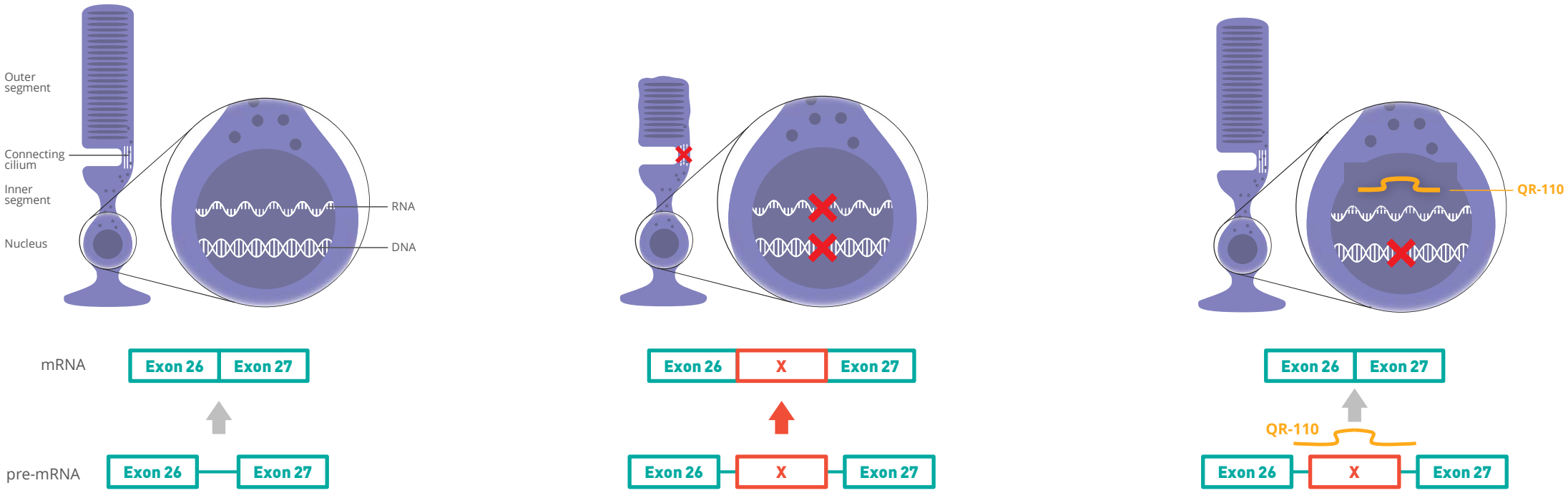
LCA10 Clinical Phenotype



- Most severe form of early childhood blindness
- Very early severe vision loss with onset in the first months of life
- Symptoms include sensory nystagmus (involuntary eye movement), amaurotic pupils, oculo-digital signs, and absent electrical signals on electroretinogram (ERG).
- Is associated with a cone-sparing macular presentation

QR-110 for LCA10

Splice correction for p.Cys998X CEP290 mRNA



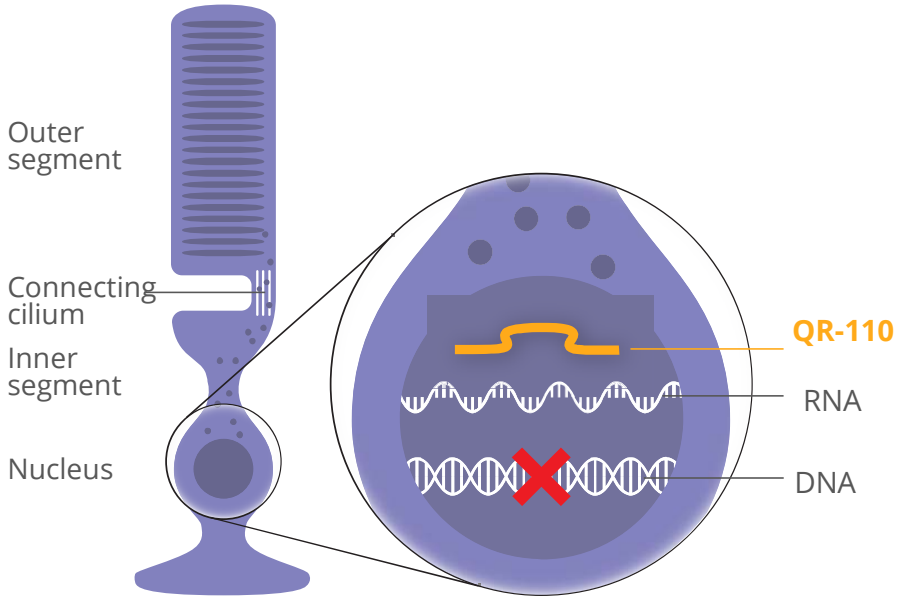
In wild-type cells CEP290 maintains cilium structure and enables normal protein transport

In p.Cys998X-LCA10 cells protein transport is hampered and the outer segment degenerates

Exclusion of the cryptic exon from the mutated mRNA leads to wild-type CEP290 protein

QR-110 for LCA10

Splice correction for p.Cys998X CEP290 mRNA



Molecular Therapy: Nucleic Acids

Antisense Oligonucleotide (AON)-based Therapy for Leber Congenital Amaurosis Caused by a Frequent Mutation in *CEP290*

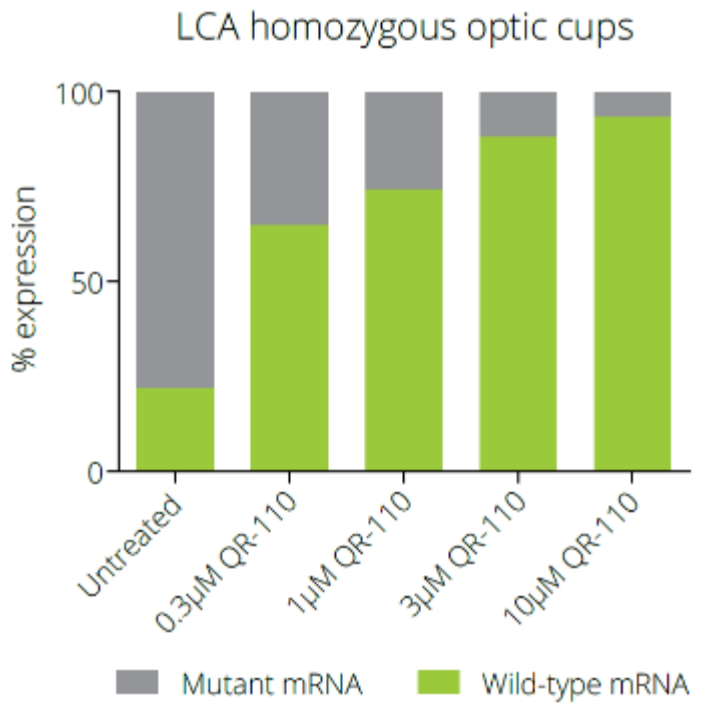
QR-110 - Asset Characterization

- Single stranded 17-mer RNA oligonucleotide
- P=S and 2'O-Me chemically modified for stability and uptake
- Well understood MoA
- Designed to target pCys998X CEP290 mutation
- IVT administration, no detectable systemic exposure

QR-110 - Data

- >95% mRNA editing efficiency in human eye cups
- Demonstration of CEP290 full-length protein by blot
- Ability to increase both number and length of cilia in LCA eye cups (functional response
- Ability to distribute to photoreceptor layer after IVT injection
- IND and CTA open
- Fast-Track Designation granted

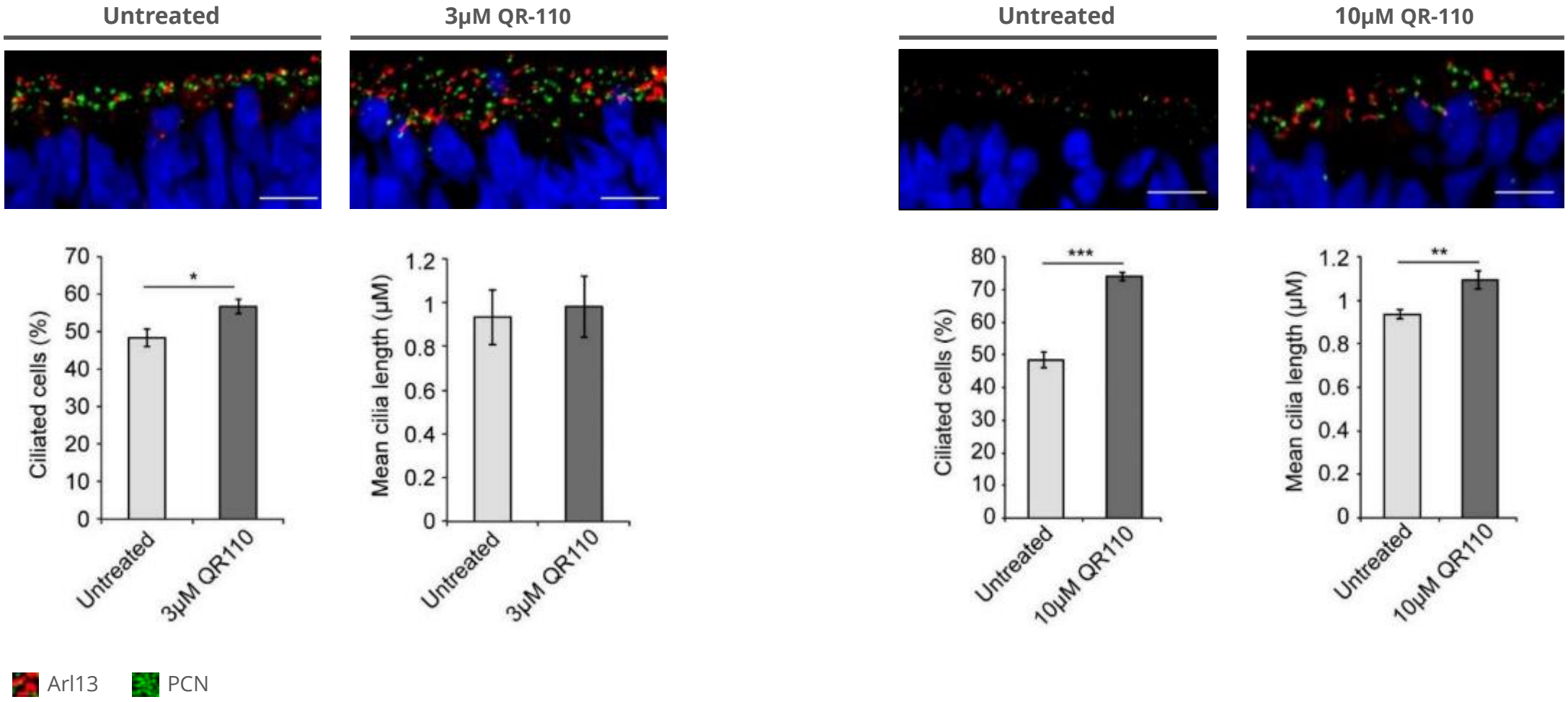
QR-110 corrects CEP290 mRNA in LCA patient Eye cups



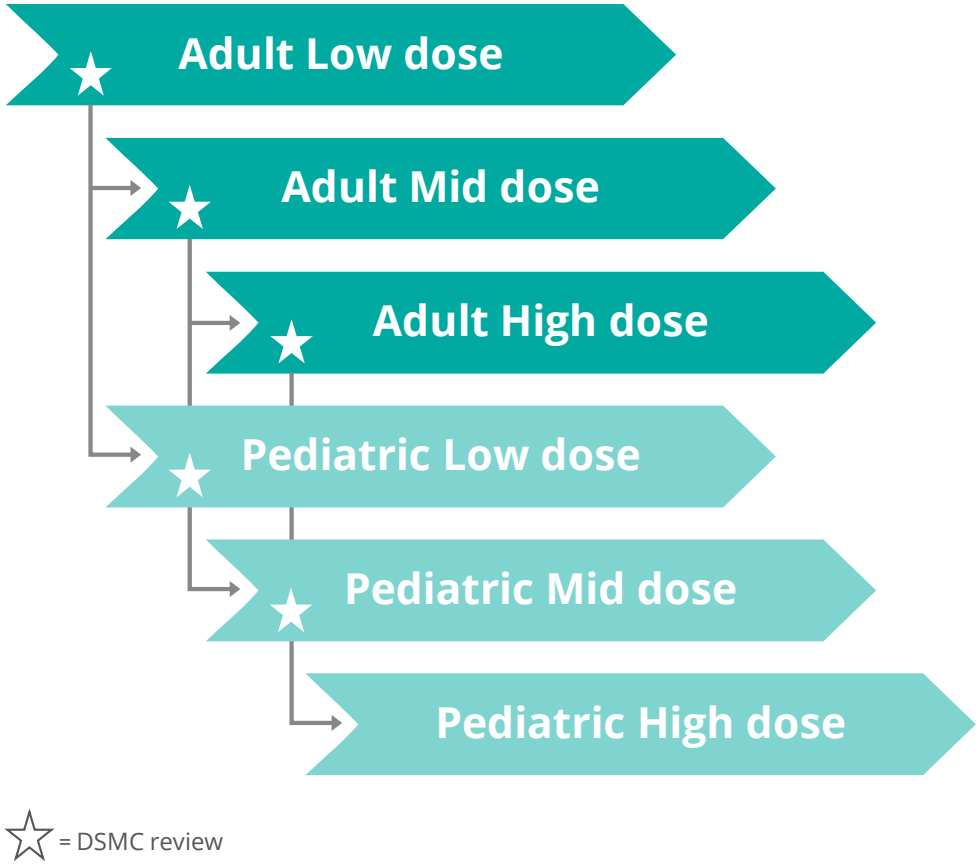
Key takeaways:

- QR-110 shows strong pre-clinical PoC in eye cup retinal organoid model
  - Restoration of WT protein in dose dependent way was observed
  - QR-110 restored QT mRNA in dose dependent way
- Optic cup model is sophisticated in vitro retinal structure

QR-110 treatment in optic cups shows increase in incidence and length of cilia



Clinical study design – PQ-110-001

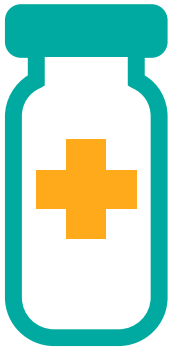


- Twelve p.Cys998X LCA10 patients; adults and children (>6yrs)
- Intravitreal injections in one eye
- Participating sites: major sites in EU (UGhent) and US (UPenn, UIowa)
- Primary endpoints:
  - Safety, tolerability and pharmacokinetics
- Exploratory efficacy:
  - FST, mobility testing, visual acuity, OCT, PRO, ERG, nystagmus tracking, pupilometry)
- **IND open**
- **FDA Fast-track designation**
- **CTA open (BE)**

QRX-421

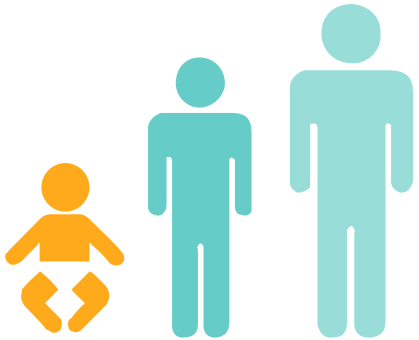
Splice correction for Usher's syndrome (Exon 13 skip)

QR-421 for Ushers

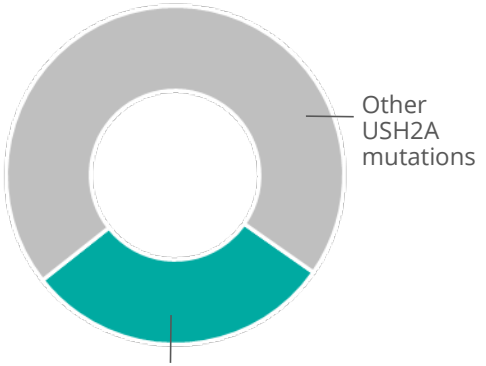


No therapy available

Eye



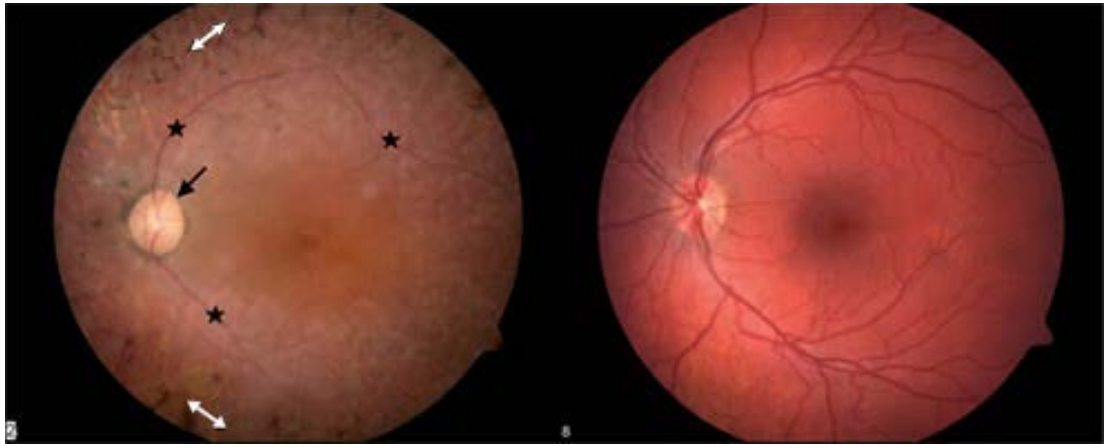
Early onset



~12,000 patients with Exon 13 in USH2A in Western world

Clinical phenotype USH2A (RP) or NSRP

USH2A Symptoms: Pale optic nerve, thin vessels

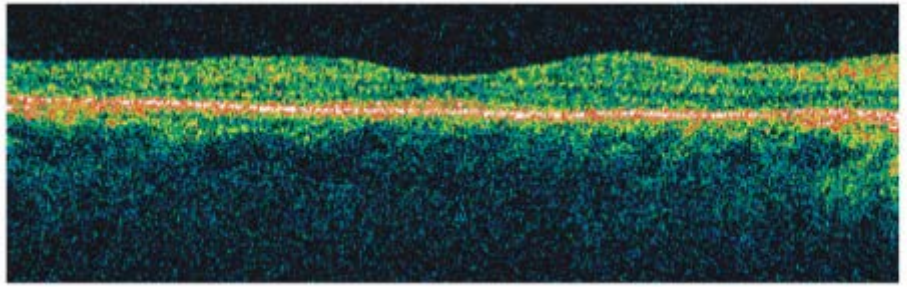


USH2A Normal

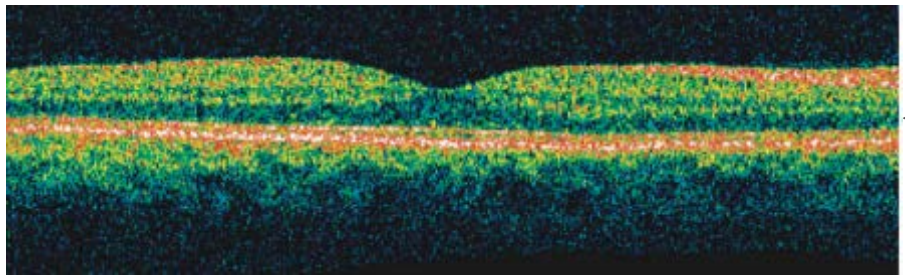
- First manifestation is night blindness (Nyctalopia)
- Gradual loss of peripheral retina resulting in tunnel vision.
- Subsequent loss of central (macula) vision resulting in complete blindness
- Variable age of onset, but disease normally evident in late teen/early 20s
- Is associated with a cone-sparing macular presentation

From Sandberg et al. 2008

Degeneration of Outer Nuclear Layer (ONL)



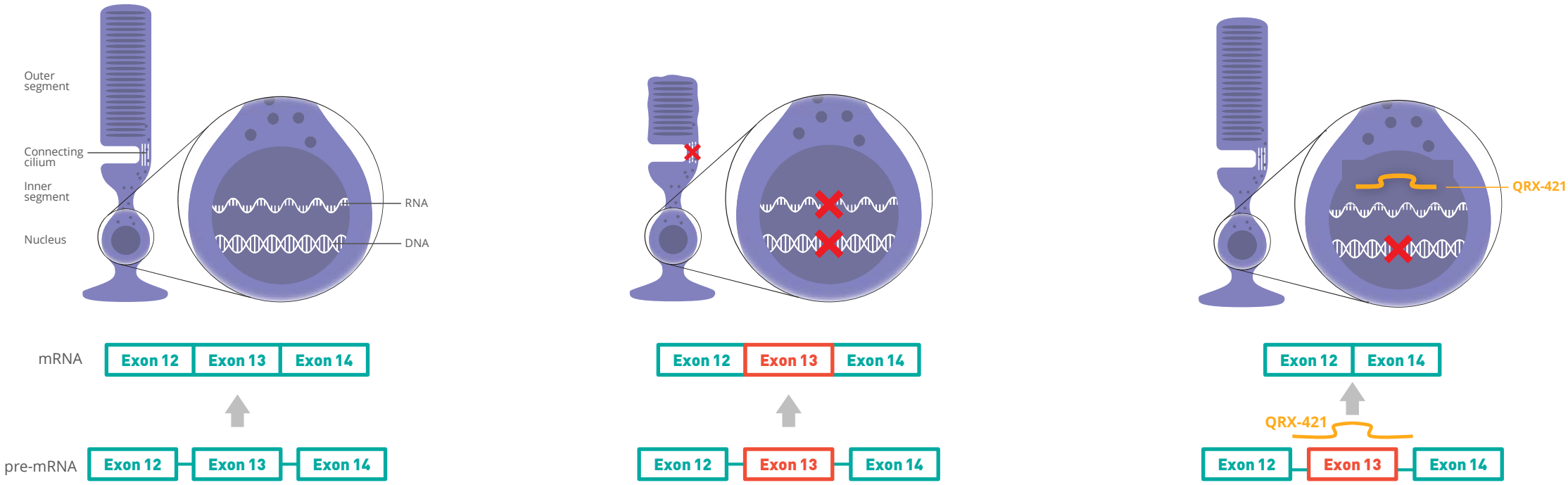
USH2A



Normal

QRX-421 for Usher's syndrome

USH2A exon 13 splice correction



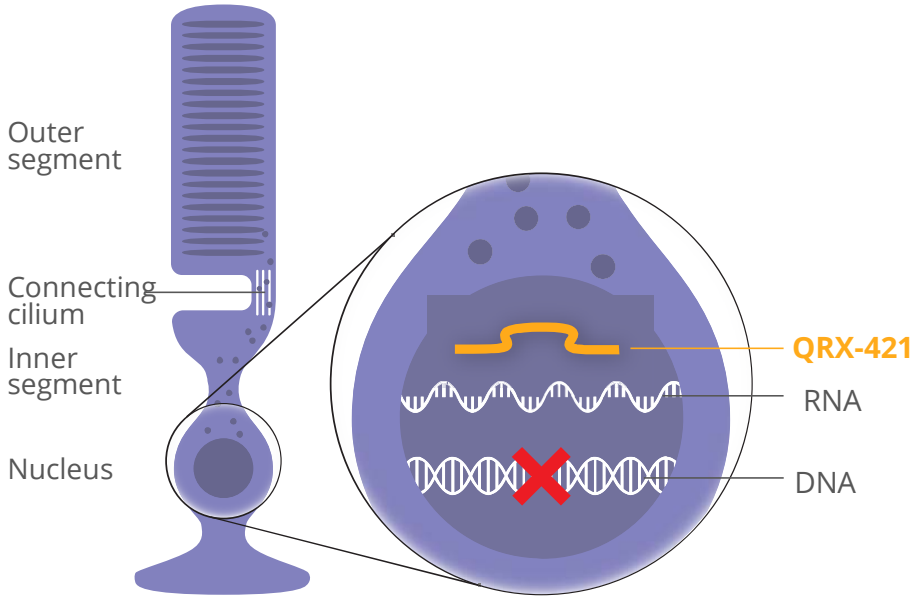
In wild-type cells Ush2A protein enables protein transport through the connecting cilium

In cells with the mutation Ush2A protein is not active hampering protein transport through the cilium

Exclusion of mutated exon leads to restoration of functionality of Ush2a

QRX-421 for Usher's syndrome

USH2A exon 13 splice correction



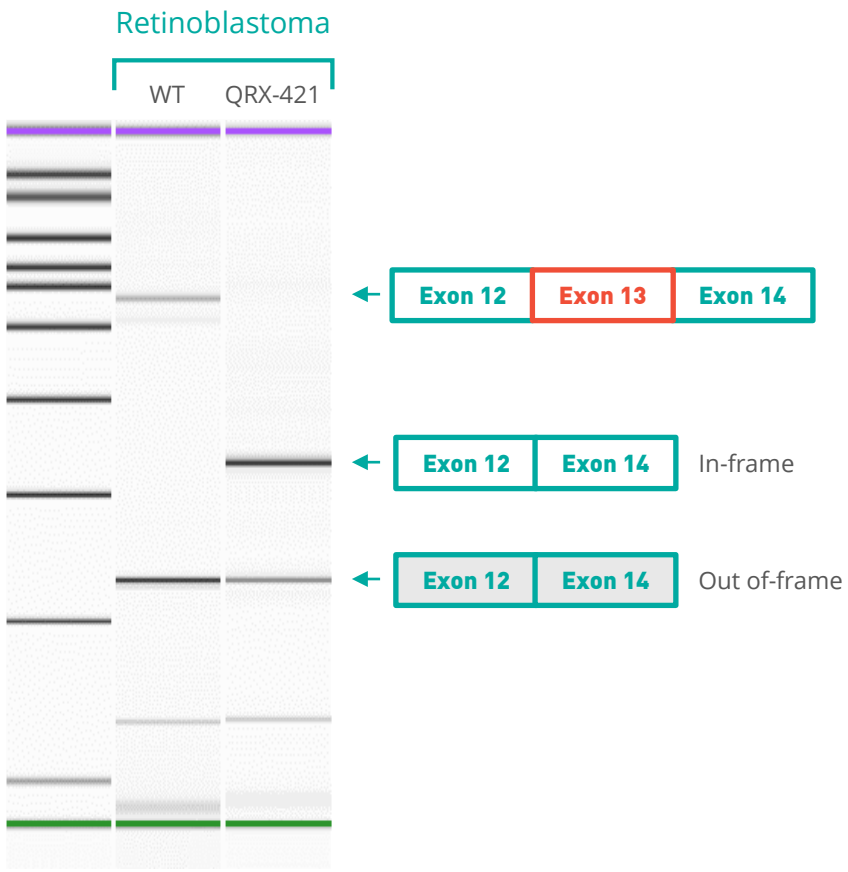
QRX-421 - Asset Characterization

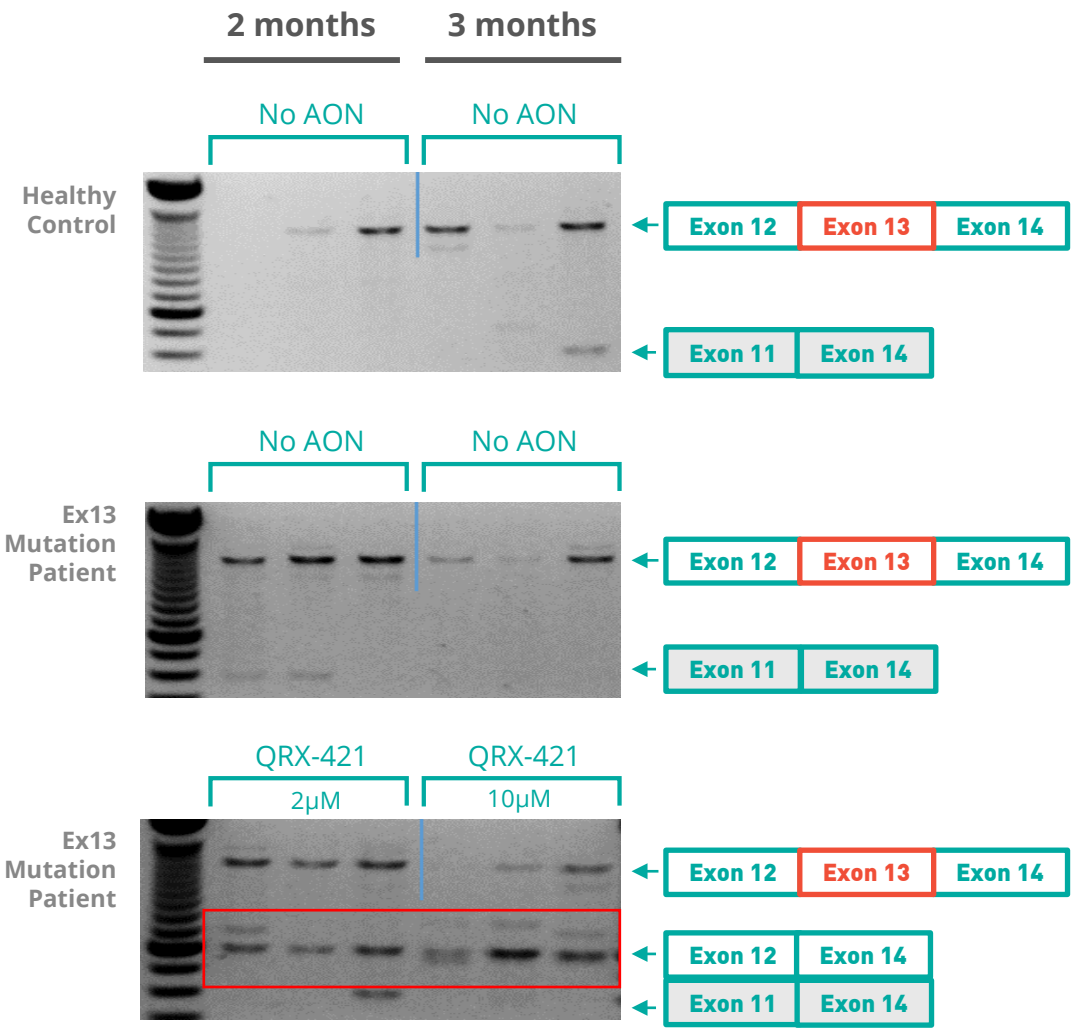
- Single stranded 21-mer RNA oligonucleotide
- P=S and 2'O-Me chemically modified for stability and uptake
- Well understood MoA
- Designed to target USH2A exon 13 mutations
- IVT administration, based on studies with LCA QR-110 likely no detectable systemic exposure in animals

QRX-421 - Data

- Strong effect in mediating Ex13 deletion, minimizing Ex13/Ex12 deletion in patient derived optic cups
- Ability to generate Usherin protein which is correctly localized to the retina in Ex13 mutant fish (tool)
- Restores lost ERG in Ex13 mutant fish (functional response)
- Ability to distribute to photoreceptor layer after IVT injection

QRX-421 mediated exon 13 skip in vitro and in optic-cups



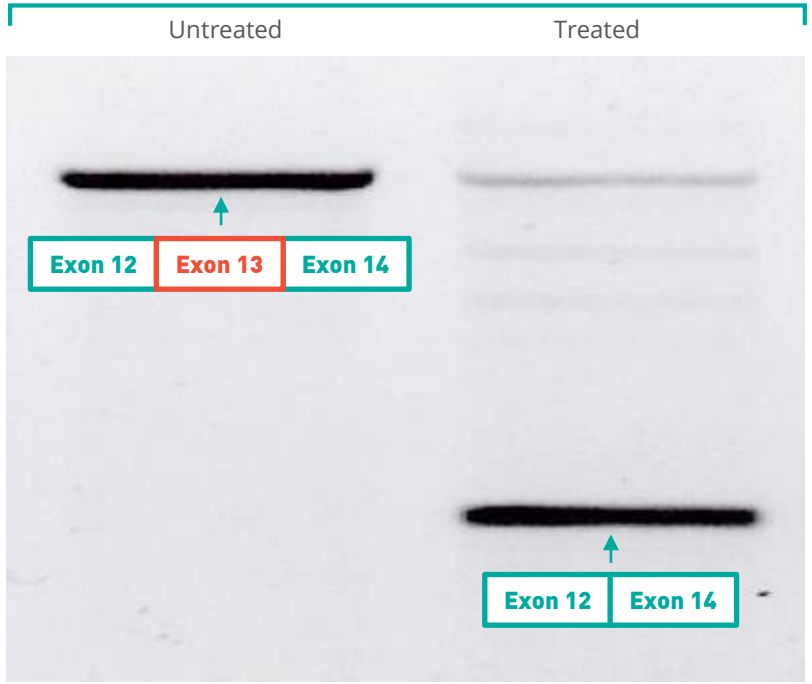


Erwin van Wijk, Radboudumc, Nijmegen, the Netherlands

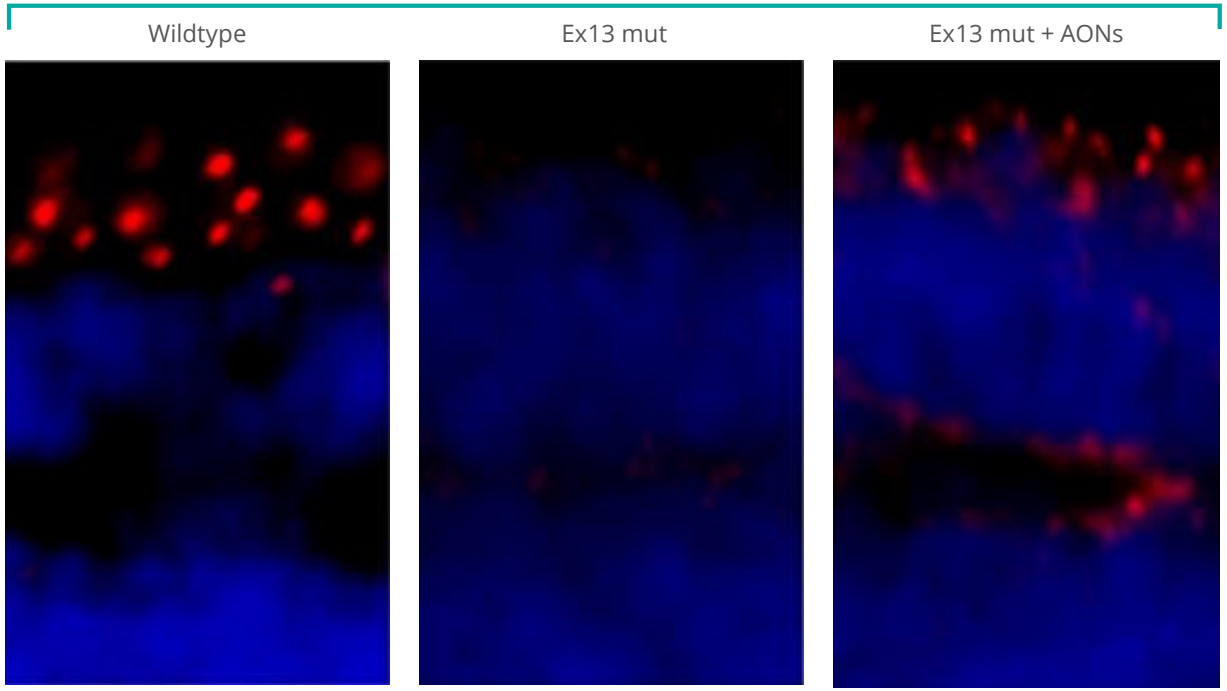
AON targeting Ex13 skip modifies mRNA and restores protein localization in Zebrafish retina

Restoration of Ush2a localization in zebrafish eyes

RT-PCR: Ush2a Ex13m -/-



Ush2a antibody in fish retina showing localization at connecting cilia



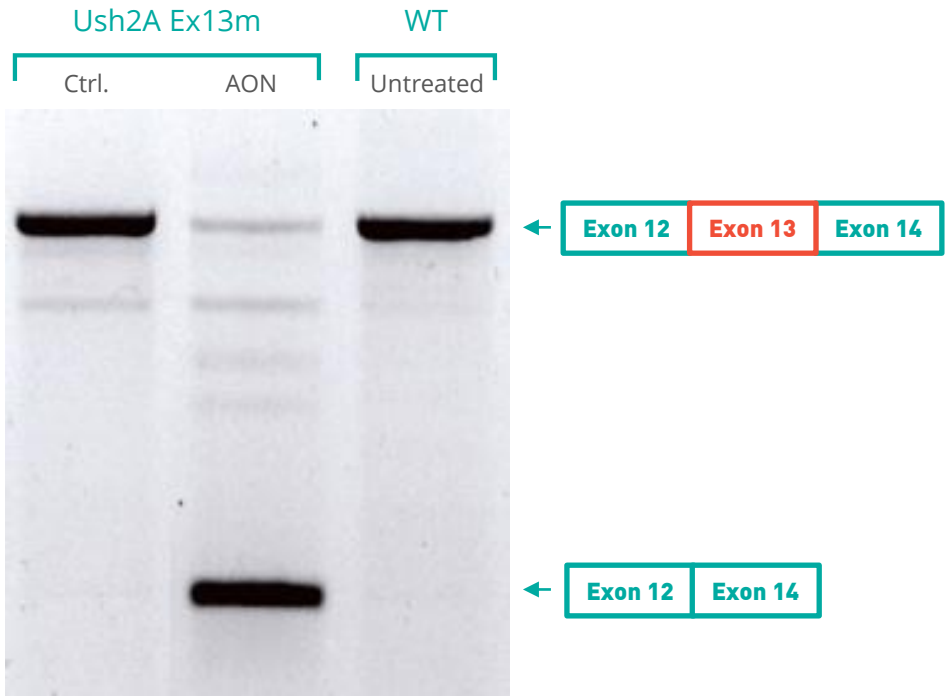
Co-staining with anti-centrin Ab showed Usherin localized at the connecting cilium

Erwin van Wijk, Radboudumc, Nijmegen, the Netherlands

Restoration of b-wave ERG to wild-type level following Exon-13 deletion

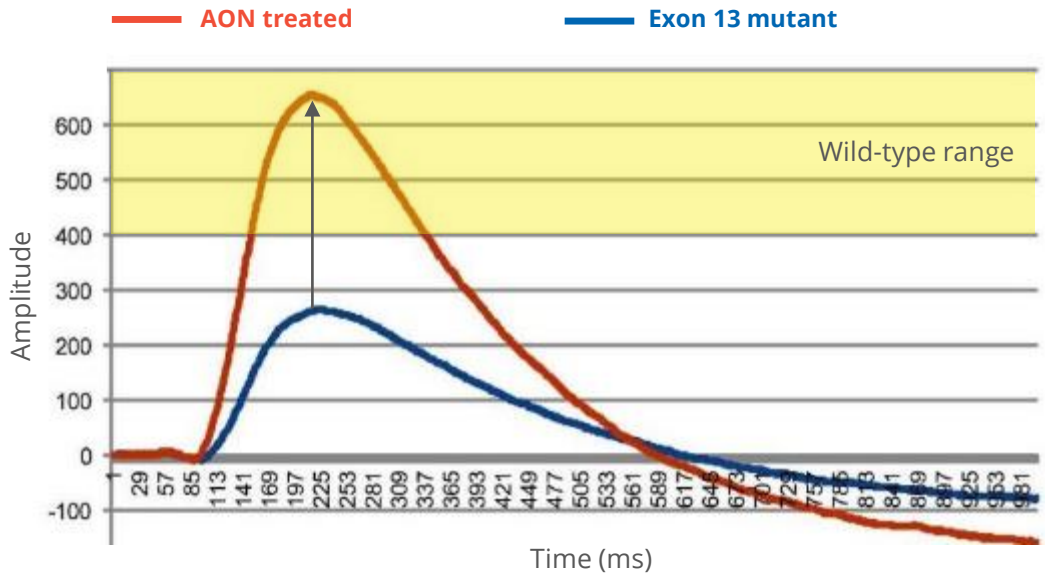
Exon 13 deleted mutant zebrafish

Exon 13 skip in zebrafish model



Bands have been Sanger sequenced and confirmed to be Ex13-skipped

AON treated zebrafish shows b-wave ERG amplitude restoration



Erwin van Wijk, Radboudumc, Nijmegen, the Netherlands

Overview: QRX-421 for USH2A Exon 13

mRNA profile restoration

mRNA profile with exon 13 skip

Local (intravitreal) delivery to the eye

Eye well validated target for oligo's

Efficient delivery to outer nuclear layer in the retina

mRNA profile restoration in eye-cups

mRNA profile shows Ex13 Skip in patient–derived eye-cups

Restoration ush2a protein levels

Significant increase in Ush2a protein levels

Functional restoration in Fish model

protein and ERG restoration established

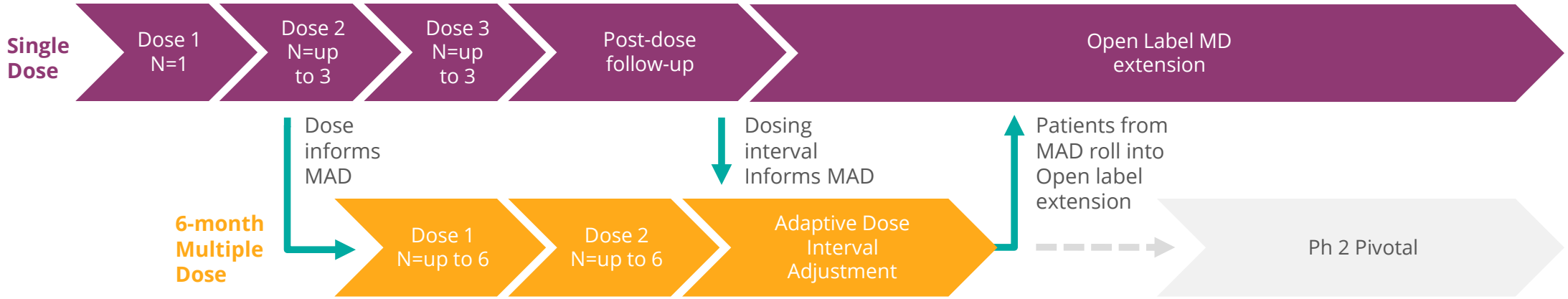
Clinical candidate selected

QR-421 selected as clinical candidate

Ready to go into Development

Ready to start IND-enabling studies

Clinical study design – QR-421 Ushers



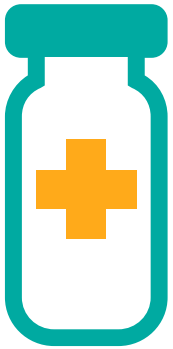
- Intravitreal Injection of "worst eye" only
- Contralateral eye and subject's baseline as controls
- Primary endpoints:
  - Safety, tolerability and pharmacokinetics
- Pharmacodynamic endpoints:
  - OCT: Photoreceptor layer thickness (focus on OS layer) starting at 2w

- Main clinical end-points: efficacy/ biological activity
  - Visual Acuity
  - Visual Field
  - Full field ERG
- **Ready to start IND-enabling studies**

QRX-411

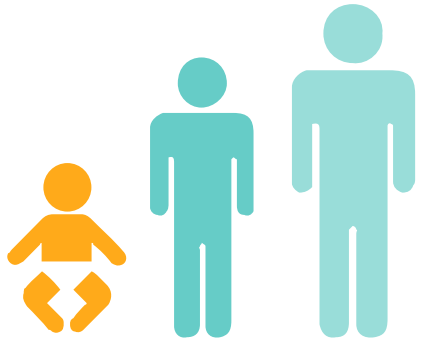
Splice correction for Usher's syndrome type II PE40

QR-411 for Ushers

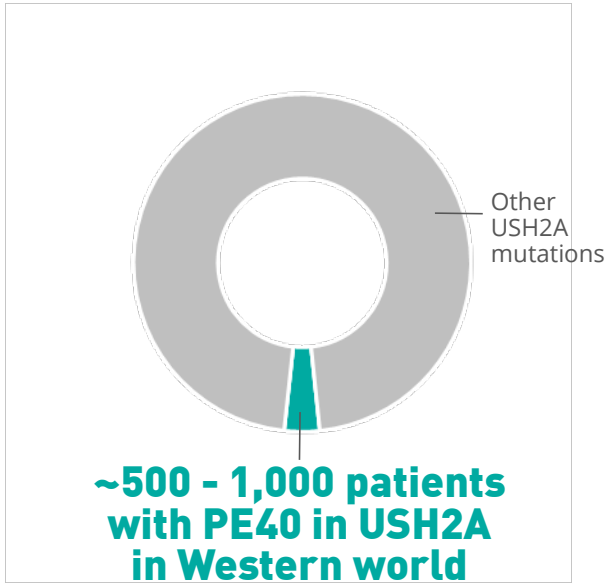


No therapy available

Eye



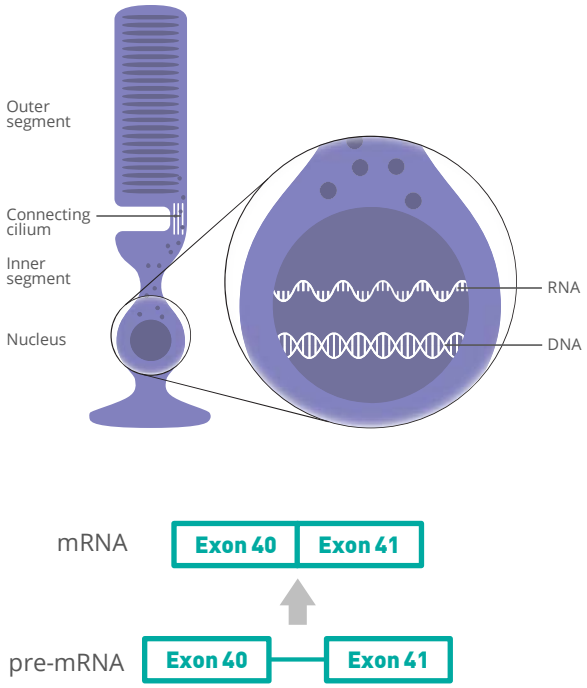
Early onset



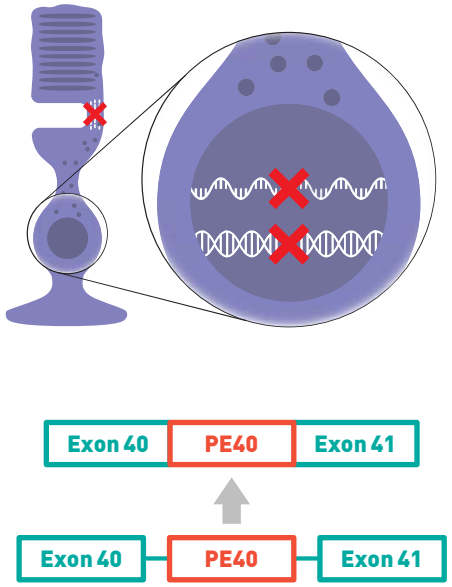
~500 - 1,000 patients with PE40 in USH2A in Western world

QRX-411 for RP in Usher Syndrome

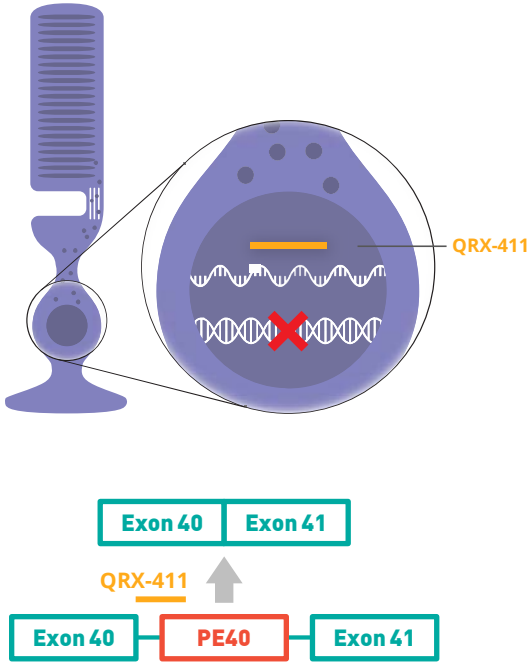
Splice correction for PE40 USH2A mRNA



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



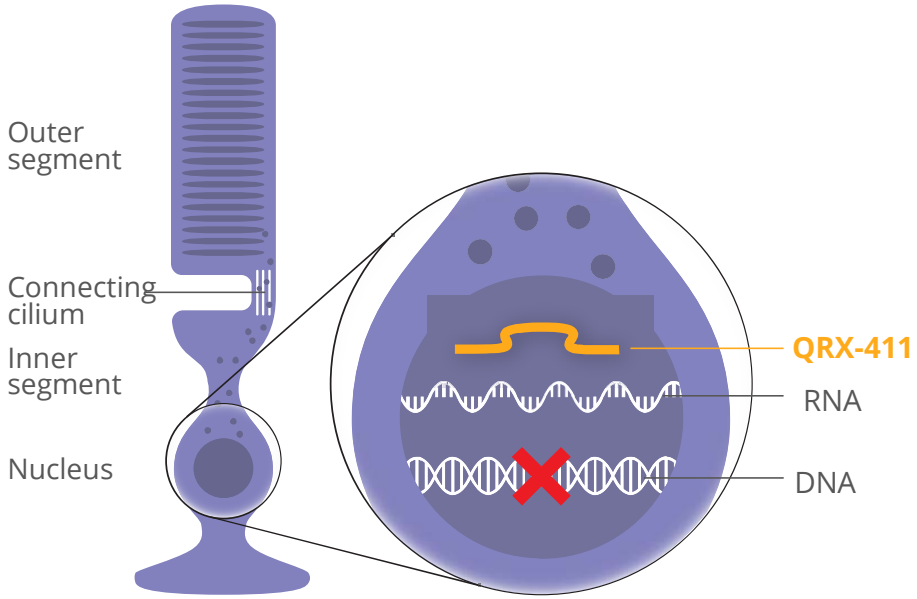
In PE40 mutant cells
protein Transport
is hampered and the outer segment degenerates



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

QRX-411 for Ushers syndrome

USH2A PE 40 splice correction



QRX-411 - Asset Characterization

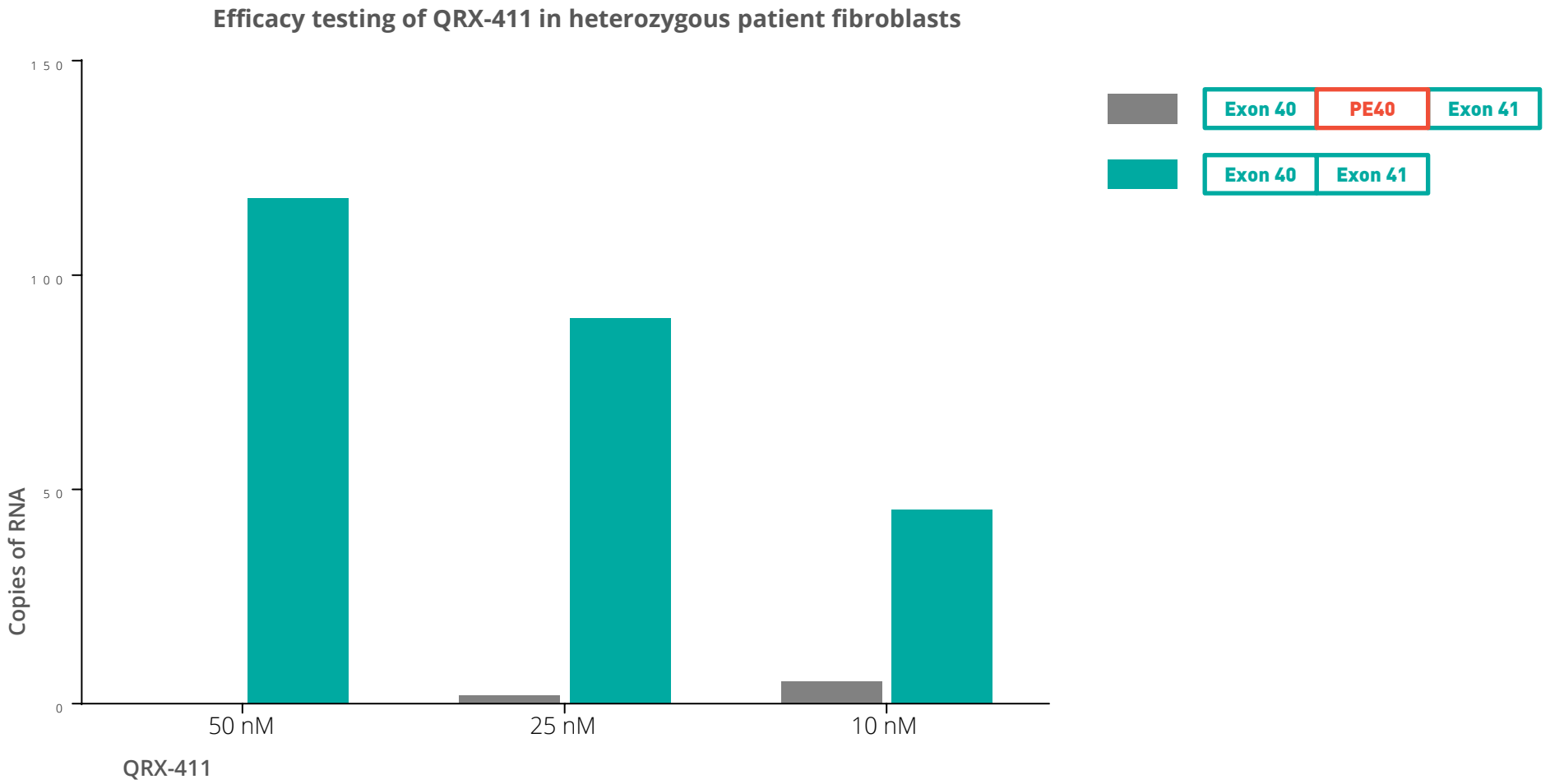
- Single stranded 20-mer RNA oligonucleotide
- P=S and 2'O-Me chemically modified for stability, safety, efficiency and uptake
- Well understood MoA
- Designed to target USH2A PE 40 mutations
- IVT administration, based on studies with LCA QR-110 likely no detectable systemic exposure in animals

QRX-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 QR-110

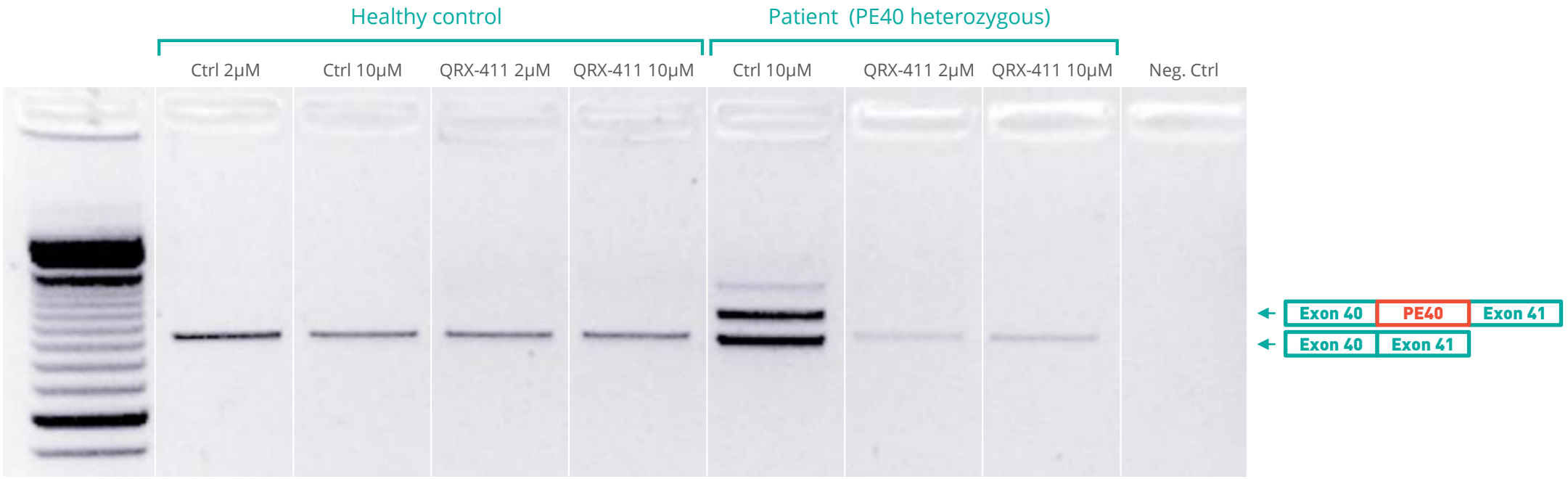
In vitro proof of concept

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



In vitro proof of concept

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



Erwin van Wijk, Radboudumc, Nijmegen, the Netherlands

Overview: QRX-411 for USH2A PE40

mRNA profile restoration

mRNA profile restored to wild-type

Local (intravitreal) delivery to the eye

Eye well validated target for oligo's

Efficient delivery to outer nuclear layer in the retina

mRNA profile restoration in eye-cups

mRNA profile shows PE40 Skip in patient–derived eye-cups

Molecular restoration in Fish model

PE40 mRNA exclusion in human KI Tg fish

Clinical candidate selected

QR-411 selected as clinical candidate

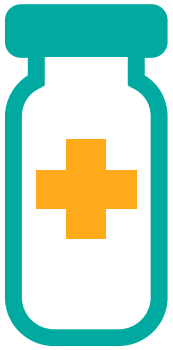
Ready to go into Development

Ready to start IND-enabling studies

QRX-1011

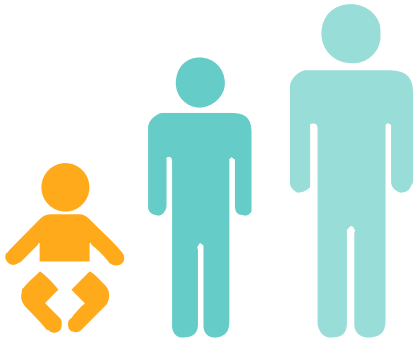
Stargardt's Disease

QR-1011 for Stargardt's Disease

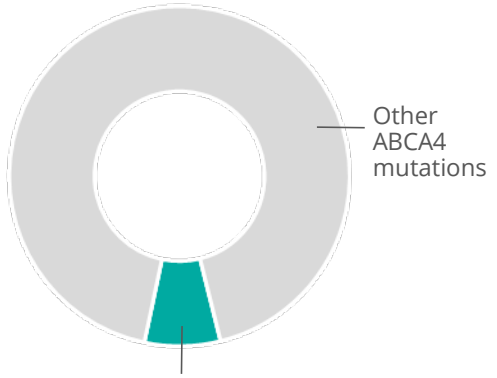


Unmet medical need

Eye



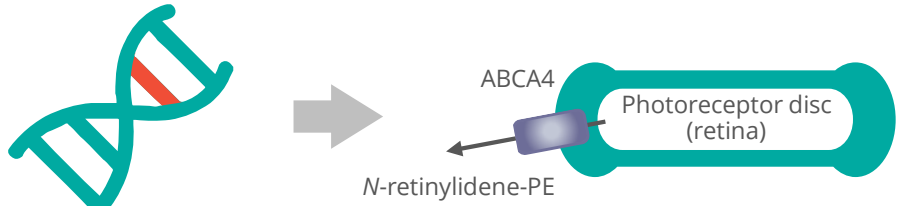
Early onset

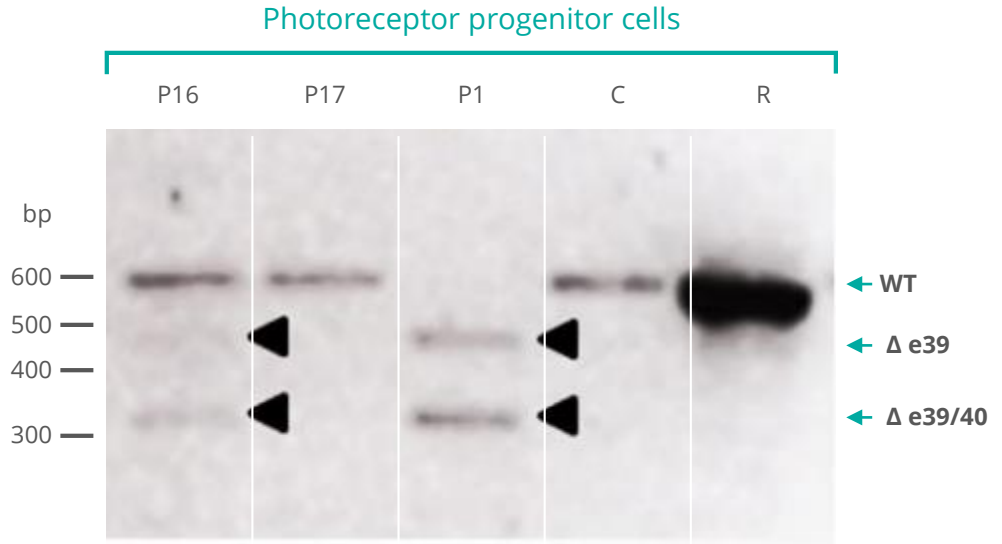


~7,000 patients with c.5461-10T>C in ABCA4 in Western world

Stargardt's Disease

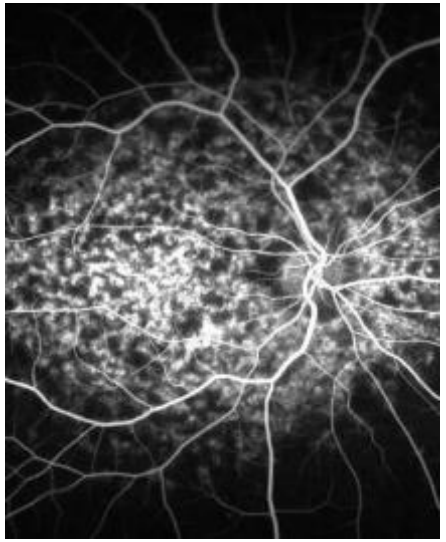
- Mutations in **ABCA4** gene destroys function of ABCA4 (> 800 known mutations in the ABCA4 causes STGD1)
- Target mutation ABCA4 c.5461-10T>C
- Approximately 7,000 patients



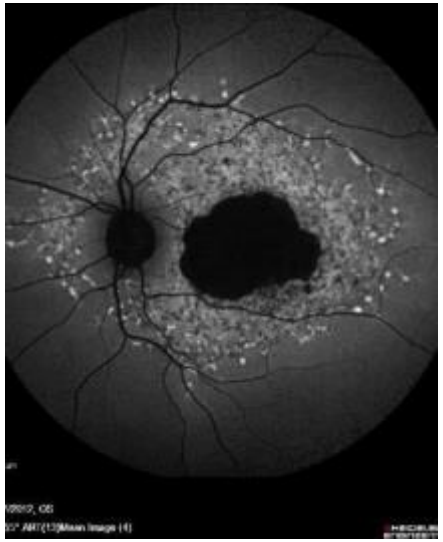


Stargardt's Disease: Clinical Phenotype

Color Fundus Photography (CFP)



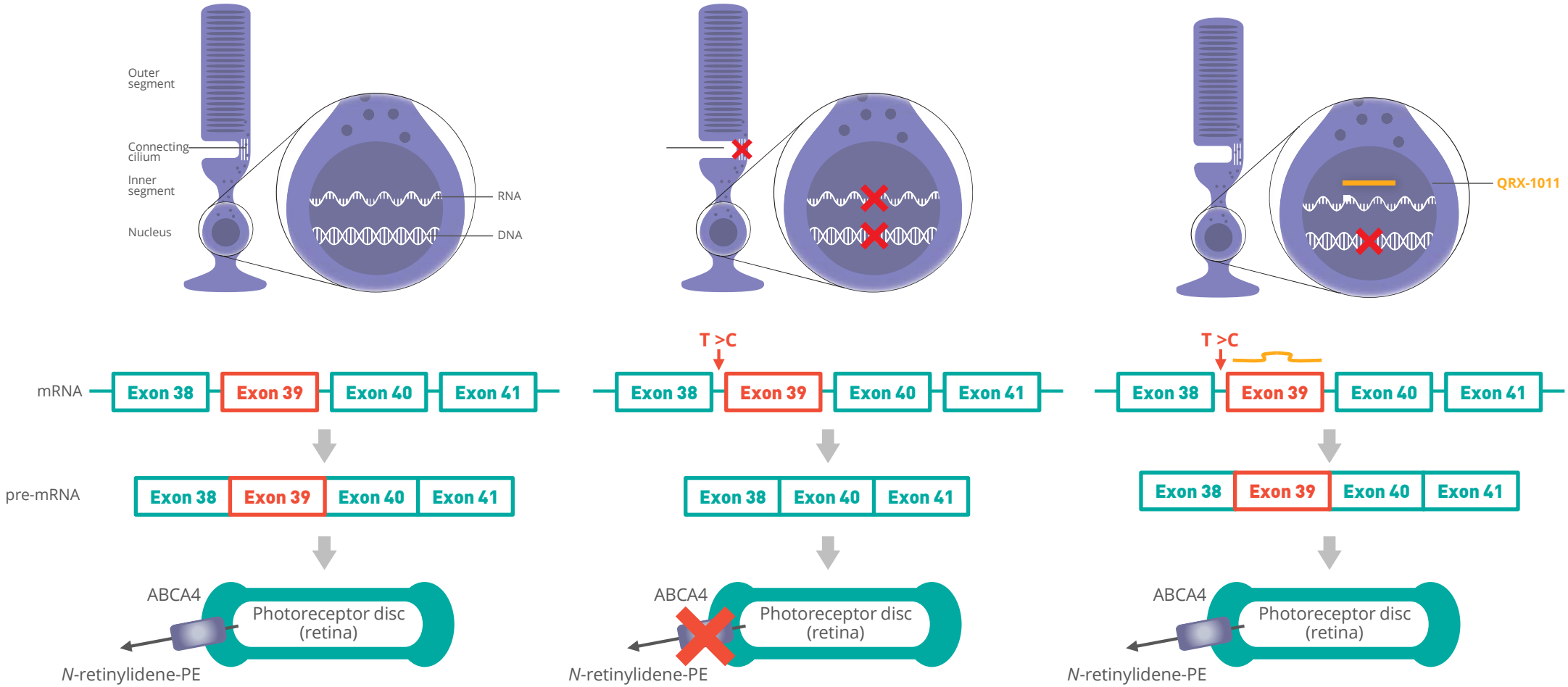
Fluorescein Angiography (FA)



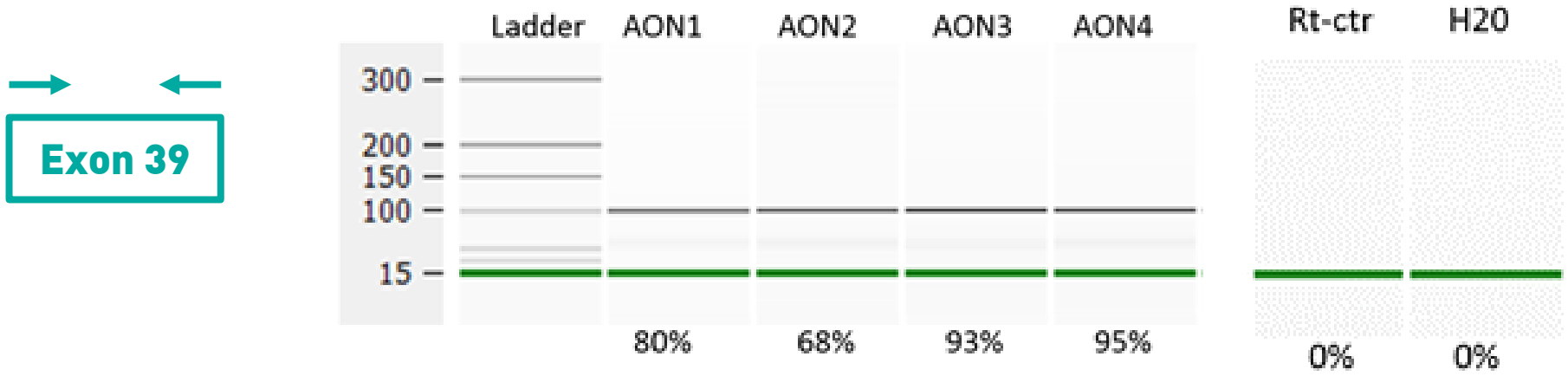
Fundus Autofluorecence (FAF)

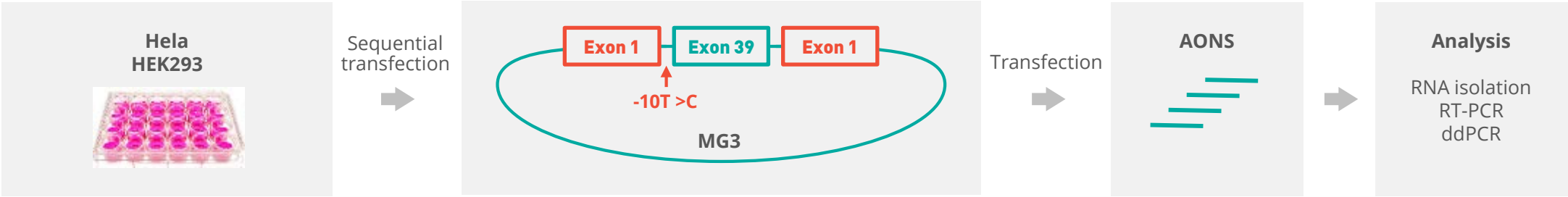
- Most frequent form of inherited juvenile macular degeneration
- Manifests as central vision loss and progresses to complete blindness
- Median onset of disease approx. 17 years
- Loss of RPE cells (scotoma)

Prevention of Exon 39 skipping- Exon inclusion



QRX-1011 Screening





Ophthalmology: QRX-1011 for Stargardt's Disease

QRX-1011 drives inclusion of Ex39 in mutant ABCA4 mRNA

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

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

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

Local (intravitreal) delivery to the eye

Eye well validated target for oligo's

Efficient delivery to photoreceptors (ONL)

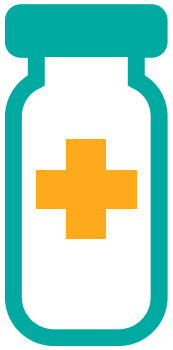
Development

Chemistry/sequence optimization ongoing

QRX-504

RNA modulation for Fuchs endothelial corneal dystrophy (FECD)

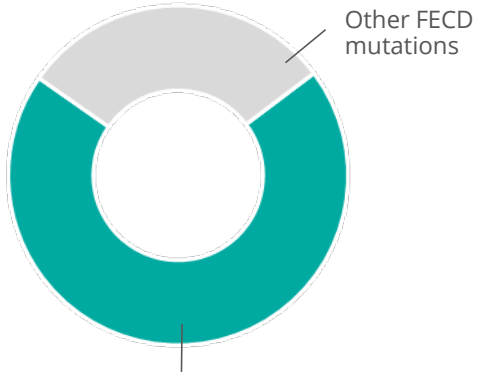
QR-504 for FECD3



Current therapy invasive and costly

Eye

Onset +50yrs



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

QRX-504 for Fuchs Endothelial Corneal Dystrophy

Progressive degeneration of the cornea

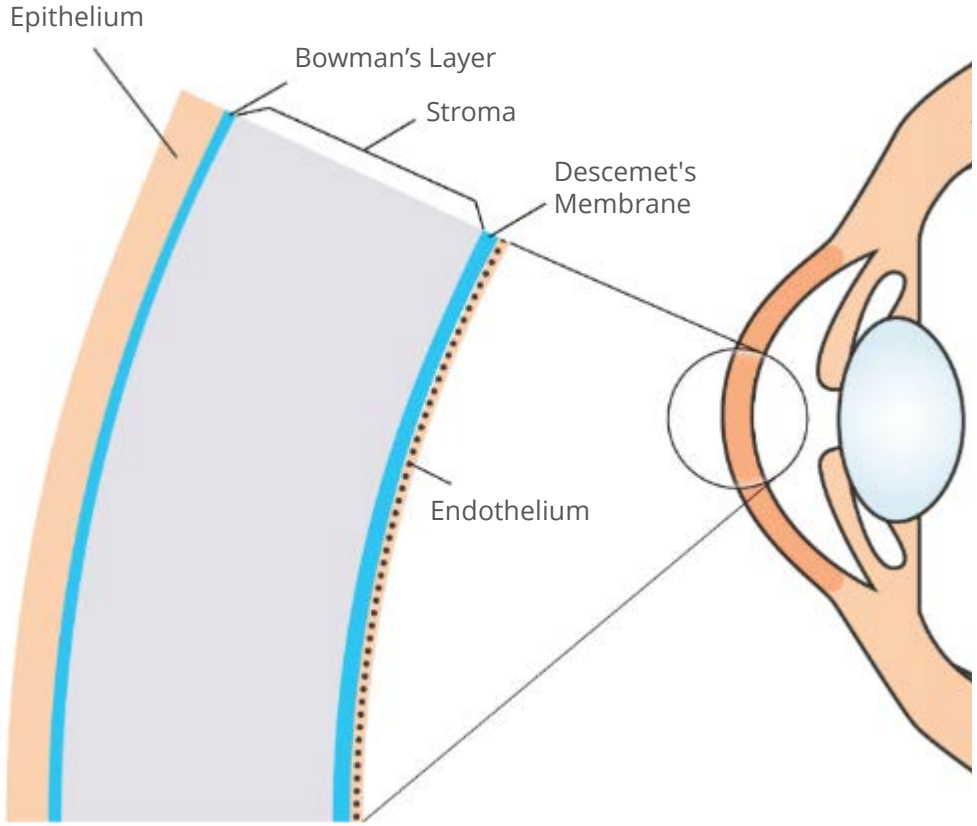
- Reduced or loss of vision due to loss (of function) of corneal endothelial cells
- ~5% of middle-aged Caucasians have guttae, a hallmark of FECD. A subset of that group develops a severe phenotype
- Disease is associated with painful corneal blisters

FECD3 caused by mutations in *TCF4* gene

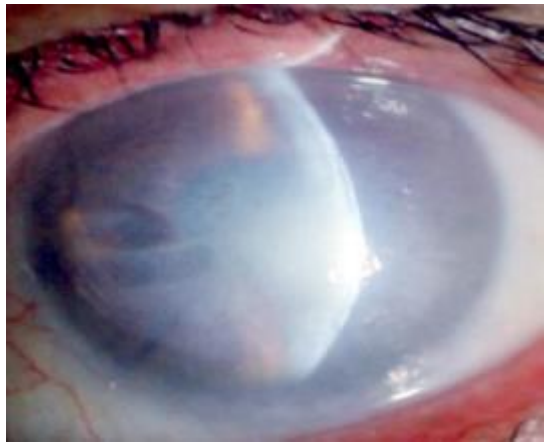
- 75% of population with guttae have TCF4 expansions
- Formation of nuclear RNA foci that sequester splicing factors
- Foci lead to loss of function of endothelium cells

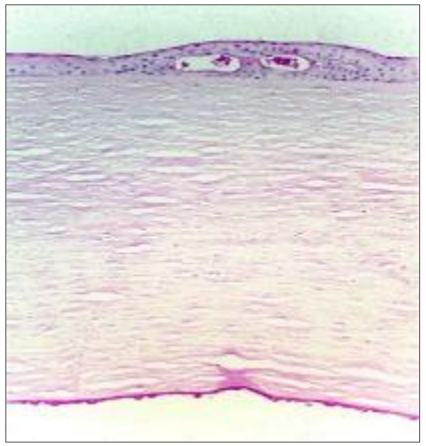
High unmet medical need

- Eye disorder, leading to blindness, 15,000 corneal transplants performed annually in the US due to Fuchs

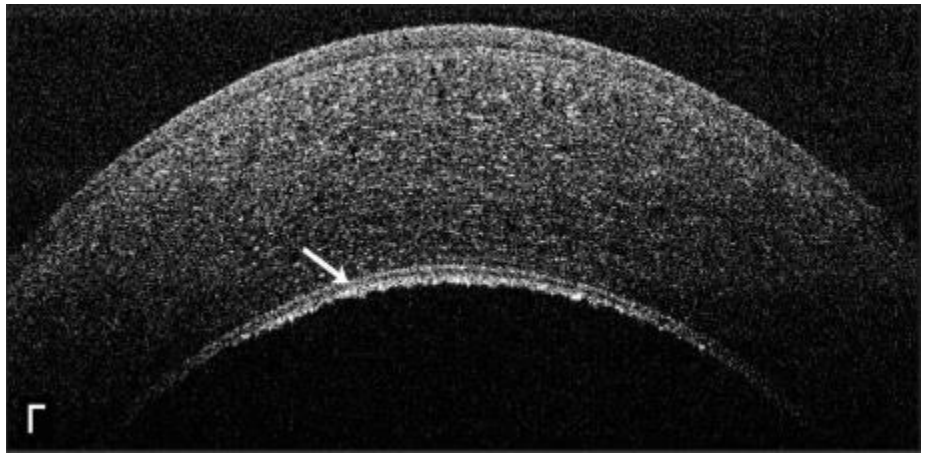


Clinical Phenotype: Fuchs Endothelial Corneal Dystrophy





Corneal edema and clouding

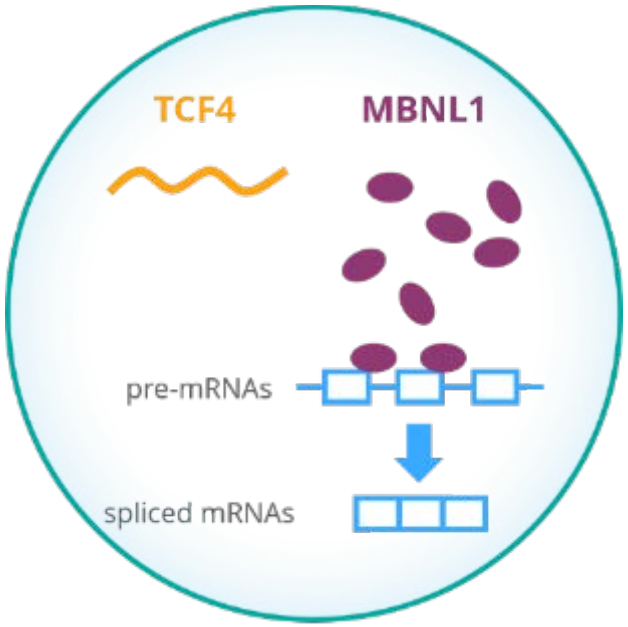


Guttae

- 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

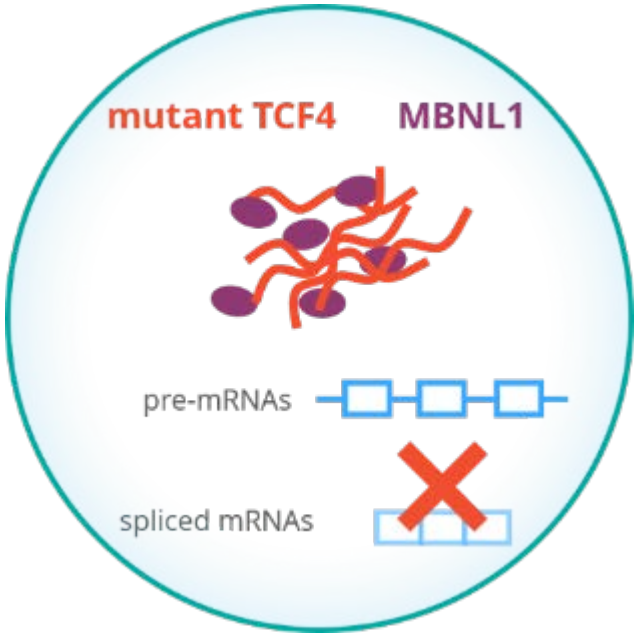
QRX-504 for FECD

Healthy



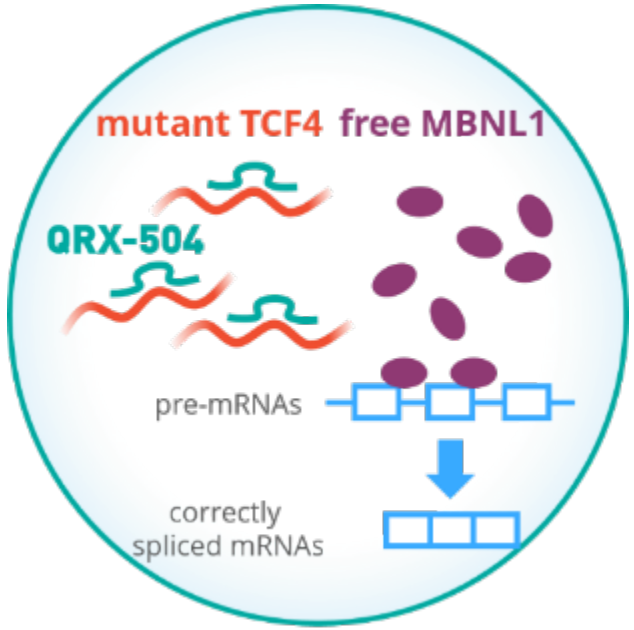
In with wild-type cells, MBNL1 protein regulates splicing of many RNAs

FECD



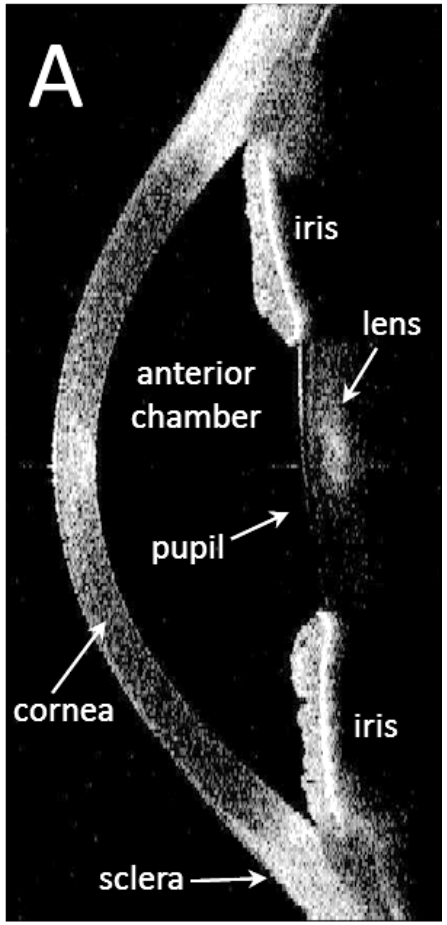
Mutated TCF4 RNA and MBNL1 form aggregates (foci), and splicing is disrupted

QRX-504 treated



QRX-504 targets the TCF4 RNA and releases MBNL1 to enable correct splicing of RNA

QRX-504 for FECD



QRX-504 - Asset Characterization

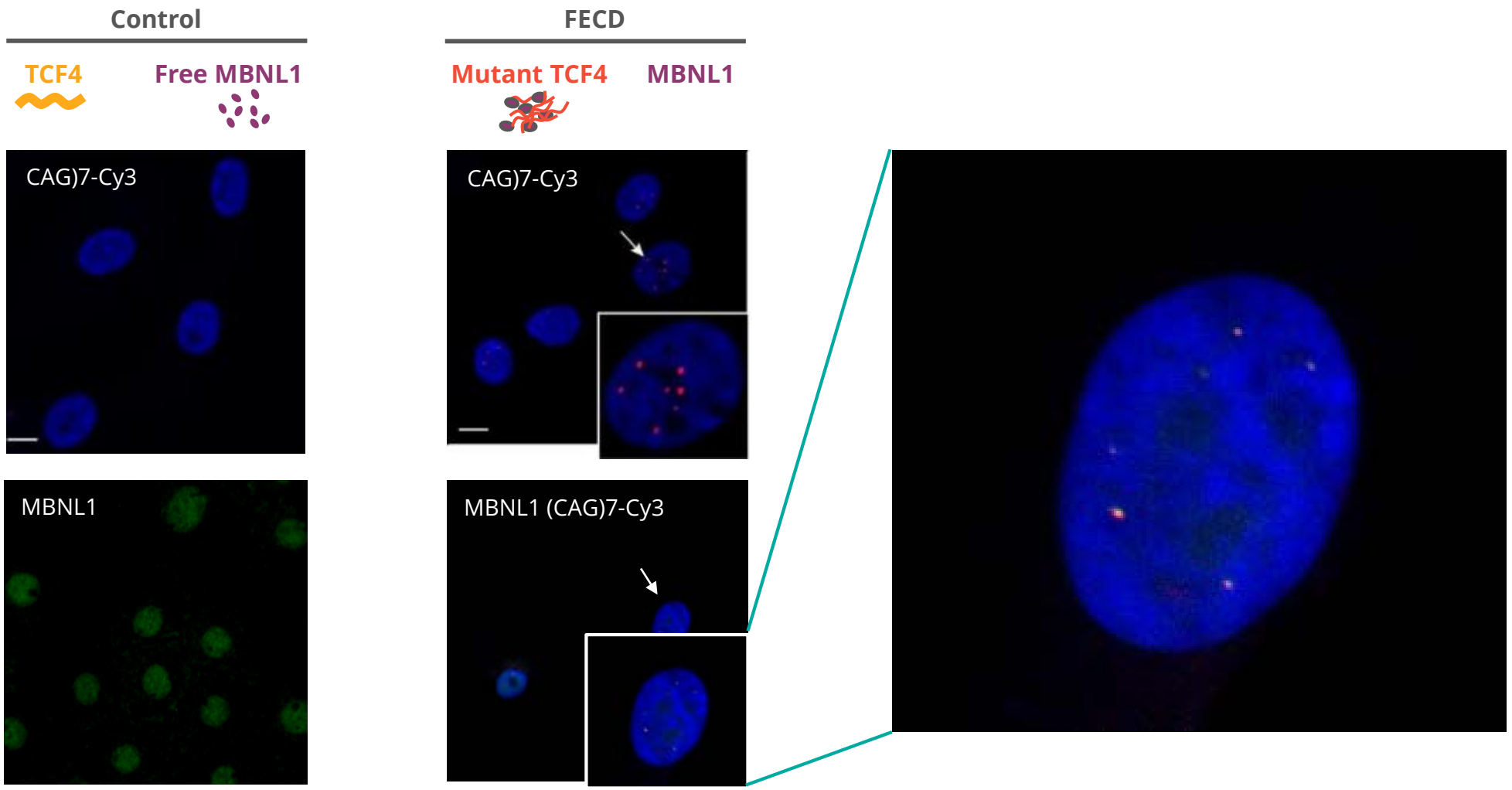
- Single stranded 21-mer RNA oligonucleotide
- Sequence and chemistry fully optimized.
- P=S and 2'O-Me chemically modified for stability and uptake
- Well understood MoA
- Designed to target nucleotide expansion in FECD3 patients caused by mutations in the TCF4 gene
- IVT administration, no detectable systemic exposure

QRX-504 - Data

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

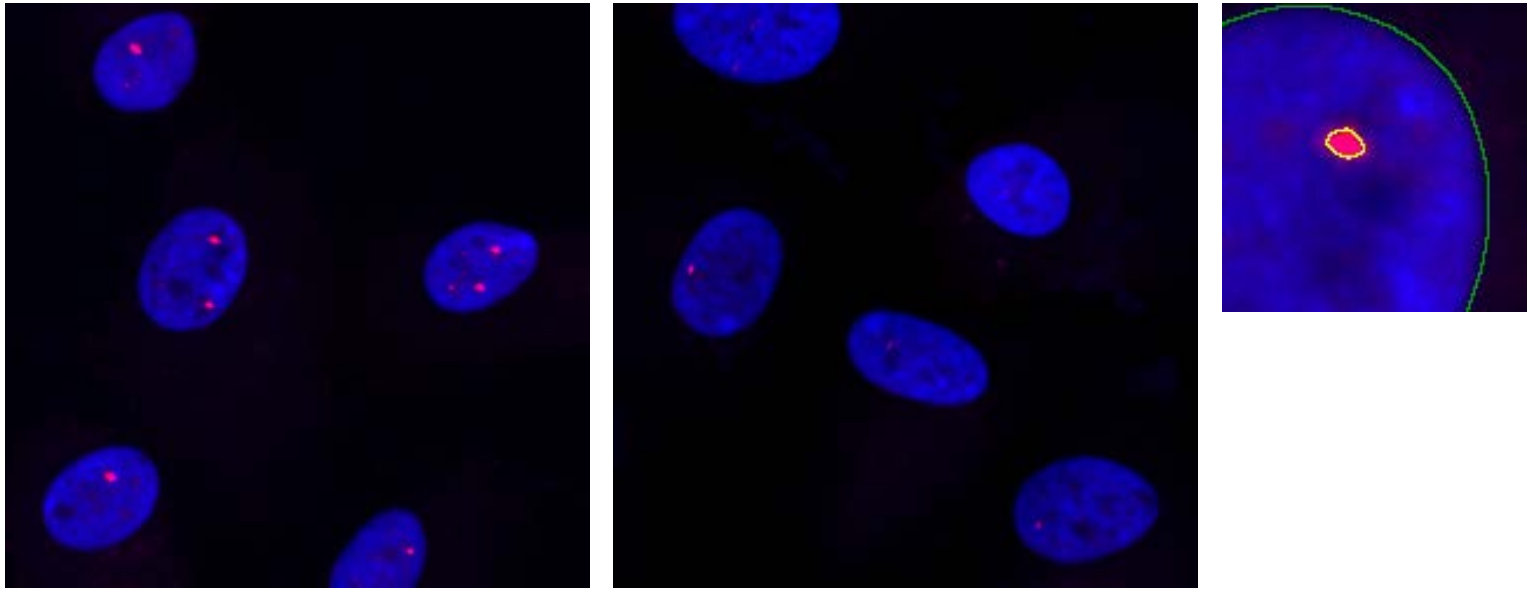
FECD patients with TCF4 mutations have RNA foci

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

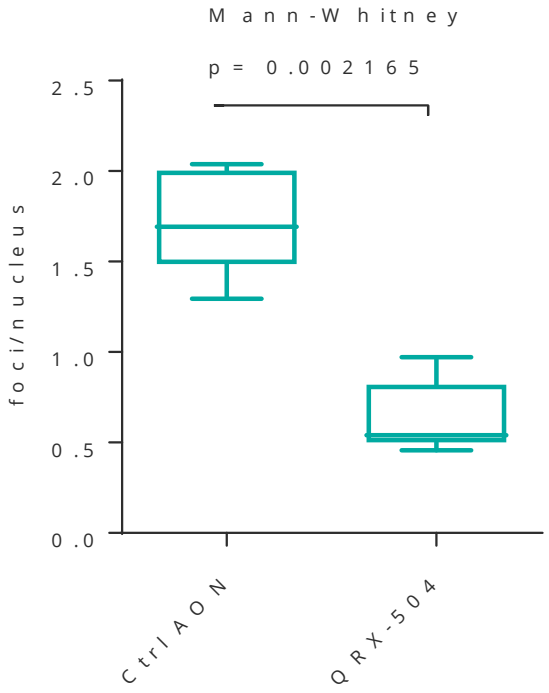


QRX-504 reduces toxic foci

Ctrl AON | QRX-504 | Automatic counting

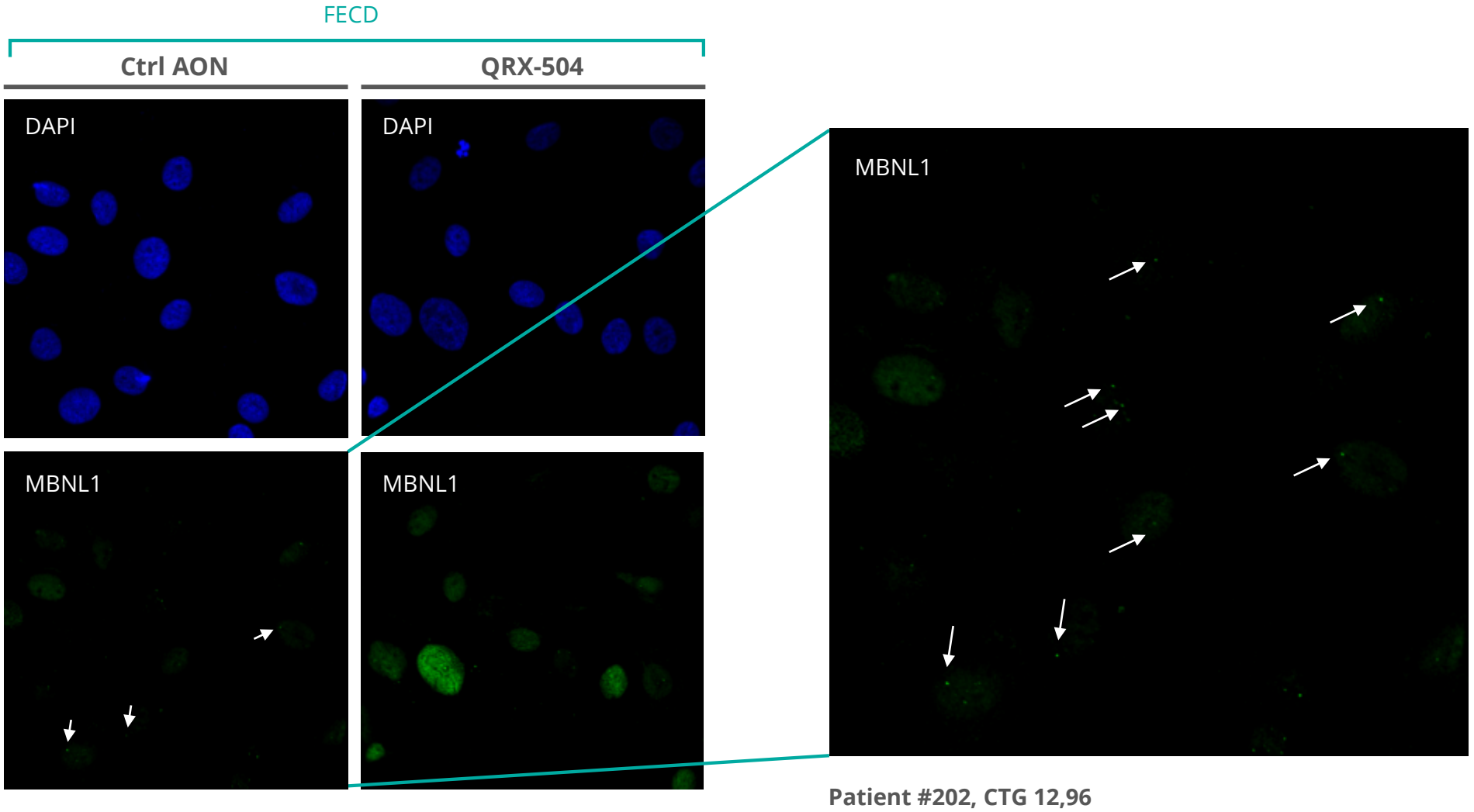


Patient #63, CTG 12/97



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

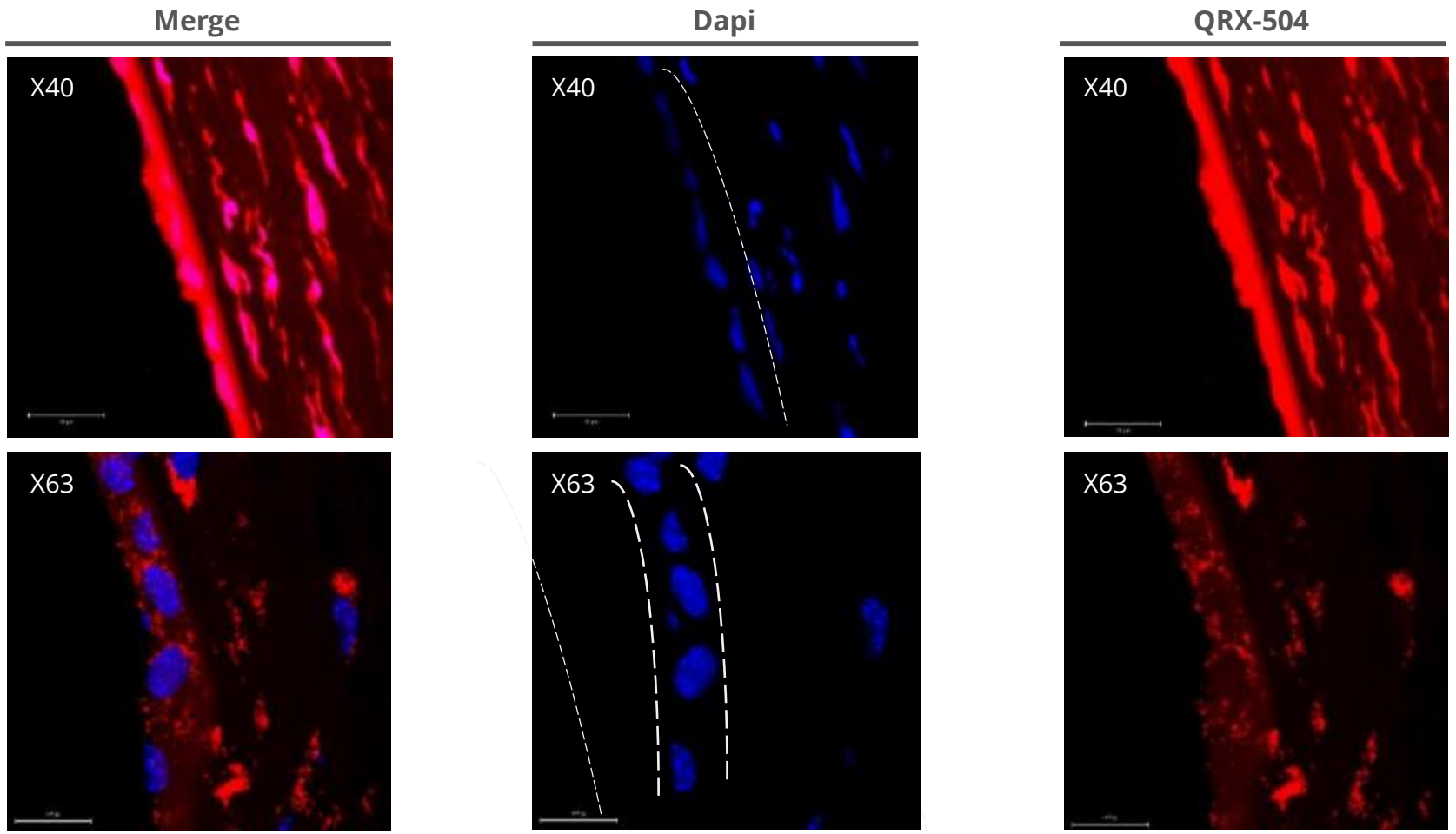
QRX-504 reduces toxic foci and MBNL-1 sequestration



Patient #202, CTG 12,96

QRX-504 delivery to corneal endothelium

IVT administered QRX-504 shows robust uptake



Cy3-labelled-QRX-504, 48h post dose, 100ug IVT dose

Ophthalmology: QRX-504 for FECD

QRX-504 reduces toxic foci

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

QRX-504 reduces sequestration of MBNL-1

MBNL-1 sequestration is reduced upon QRX-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

Ready for IND-enabling studies

Summary

Inherited Retinal Disease Program

- 1 Program in Clinical Development (LCA)
- 2 Programs at IND enabling stage (Ush)
- 1 Program at pre-clinical stage (STG)
- A number of other IRD targets in early pre-clinical evaluation

- Pre-clinical and clinical development approach is similar in all IRDs programs

- Strong focus of the use of human systems
- Use of patient eye-up models ensures translatability of validation and clinical dose rationale

Anterior Chamber Disease Program

- 1 Program at pre-clinical stage (FECD)
- Other targets under evaluation

- Strong focus of the use of human systems
- In FECD3 use of human corneal endothelial cells is key to project progression and success

FOUNDATION FIGHTING BLINDNESS

FFB Science & Clinical Research Institute Overview

JUNE 2017

Stephen M. Rose, Ph.D.

FOUNDATION FIGHTING BLINDNESS

Foundation Fighting Blindness Background

The urgent mission of FFB is to drive the research that will provide preventions, treatments and cures for people affected by the entire spectrum of retinal degenerative diseases.

FOUNDATION FIGHTING BLINDNESS

Diseases of Interest

Foundation Fighting Blindness supports research and clinical trials in orphan inherited retinal degenerations and dAMD

- Leber's congenital amaurosis
- Stargardt's Disease (juvenile macular degeneration)
- Usher syndrome
- Choroideremia
- X-linked retinoschisis
- Others (17 distinct retinal degenerations)

Definition of Orphan Disease:

Any disease affecting less than 200,000 individuals in the United States. (US National Institutes of Health) (*NIH)* Retinitis pigmentosa

Funding of dry age-related macular degeneration (AMD) is limited to areas not funded by pharma where there is potential cross-over value for juvenile macular degeneration (Stargardt's Disease).

FOUNDATION FIGHTING BLINDNESS

Foundation Fighting Blindness Background

Foundation Fighting Blindness is the world's largest non -governmental source of research funding for retinal degenerative diseases

- Funding the world's leading retinal researchers and clinicians
- Funding innovative, cutting-edge research – sight-saving potential

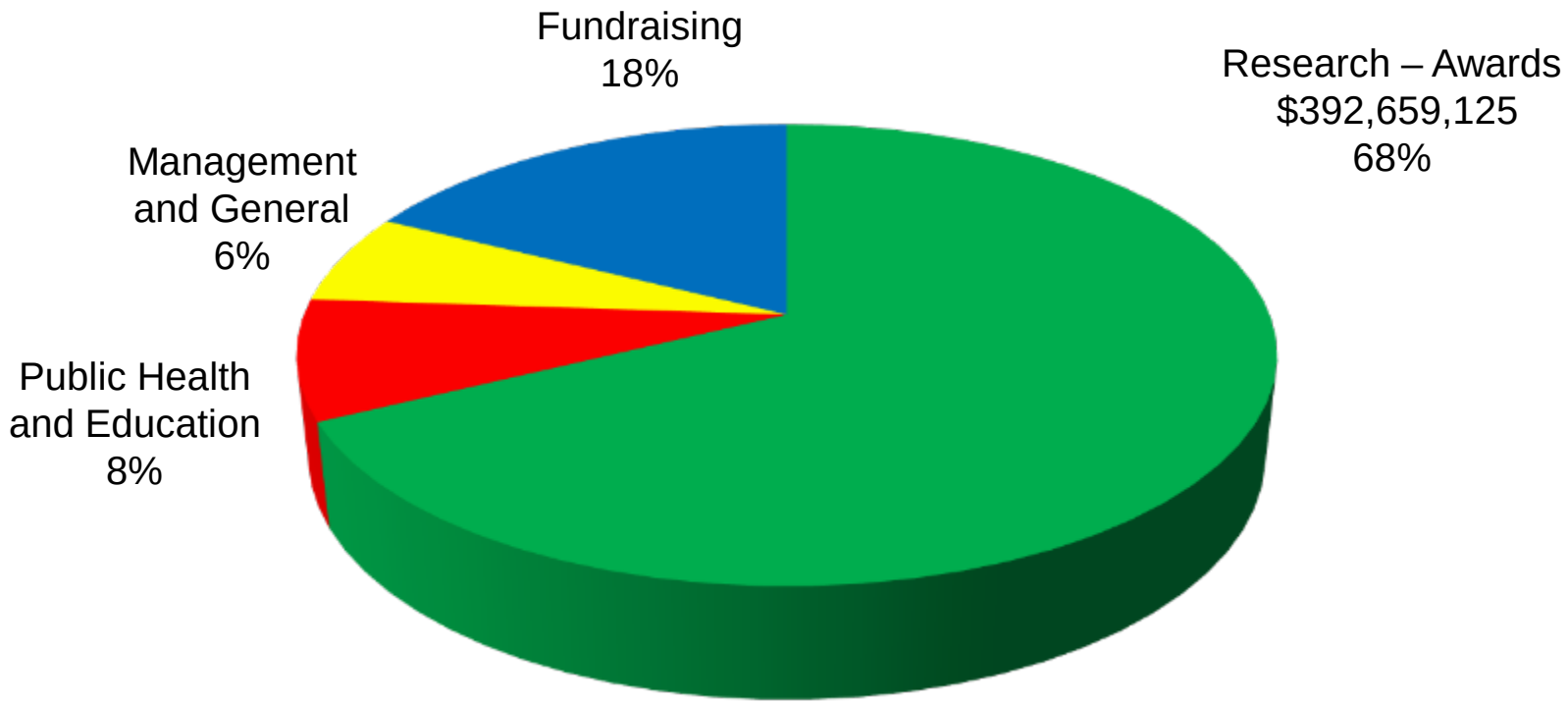
Foundation Fighting Blindness science is internationally recognized as a lead in identifying and assessing scientific breakthroughs in any and all fields that can lead to new treatments and cures for retinal degenerative diseases

Foundation Fighting Blindness has raised more than $700 million over the last 45 years to support research

- In 2016 - $21 Million allocated to support 109 research projects

QUOTE: Dr. Stephen Daiger, University of Texas-Houston, "If you were to take the 1,000 most important research papers published in the past 15 years in the field of inherited retinal diseases, 900 have authors supported by the Foundation."

Foundation Fighting Blindness Background



Historic Funding Allocation
1971 – 2016
>$700M

FOUNDATION FIGHTING BLINDNESS

One Organization – Two Entities

FFB: Foundation Fighting Blindness (Science)

- Parent organization
- Established 1971 as the Retinitis Pigmentosa Foundation
- A 501(c)3 non-profit
- Seek ROI and walk-in rights to IP
- Focus on early stage development of treatments

FFB CRI: FFB Clinical Research Institute (CRI)

- Focus on late stage development
- A 501(c)3 nonprofit
- Seek ROI on investments

Each organization has its own Board for governance

FOUNDATION FIGHTING BLINDNESS

Foundation Fighting Blindness Overall Strategy

Identify new innovative therapies

- Identify and fund research and development that accelerates innovative therapies for treatment of retinal degenerative diseases

Fund cutting edge research (Science)

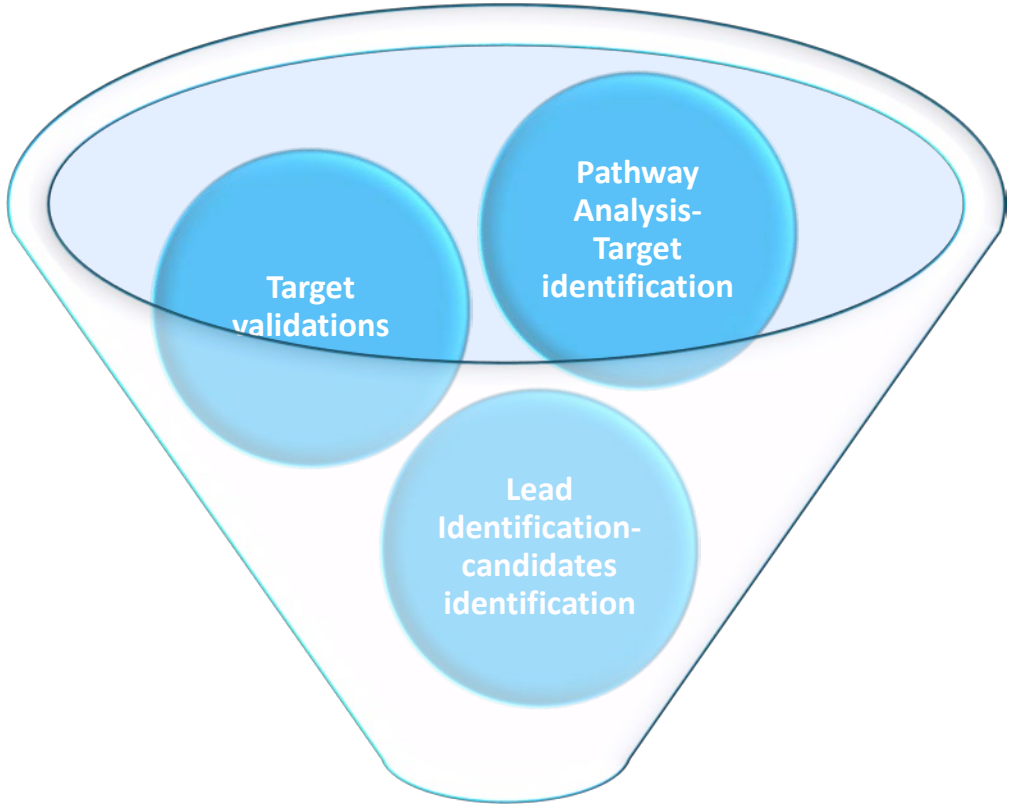
- Supports basic research in retinal cell biology based on best chance to make significant advances in knowledge and technology to bring benefit to patients
- Supports early translational research to transition the basic knowledge into genetically and mechanism of action validated targets for intervention
- Support clinical centers
- Fund career development awards

Aggressively seek development and commercialization (CRI)

- Invests in most promising interventions through proof of concept in humans- Negotiate a fair return on investment for FFB CRI to allow further intervention development (although not the first priority)
- Provide expertise, management, and funding for the intervention to be developed successfully
- help secure global commercialization partnerships with pharmaceutical and biotech companies
- Partner with Pharma or Biotech to move intervention to FDA approval and commercialization so readily available to patients
- collaborate with universities, government and industry to identify path to accelerate development of new therapeutic approaches (Identification and validation of new Clinical endpoint, conduct of Natural History Studies, ect)

FFB Impact over Time on the iRD field

- 40 years of Grant funding >$393 M
- >500 Papers & publications
- >100 Patents Filed based on FFB supported research

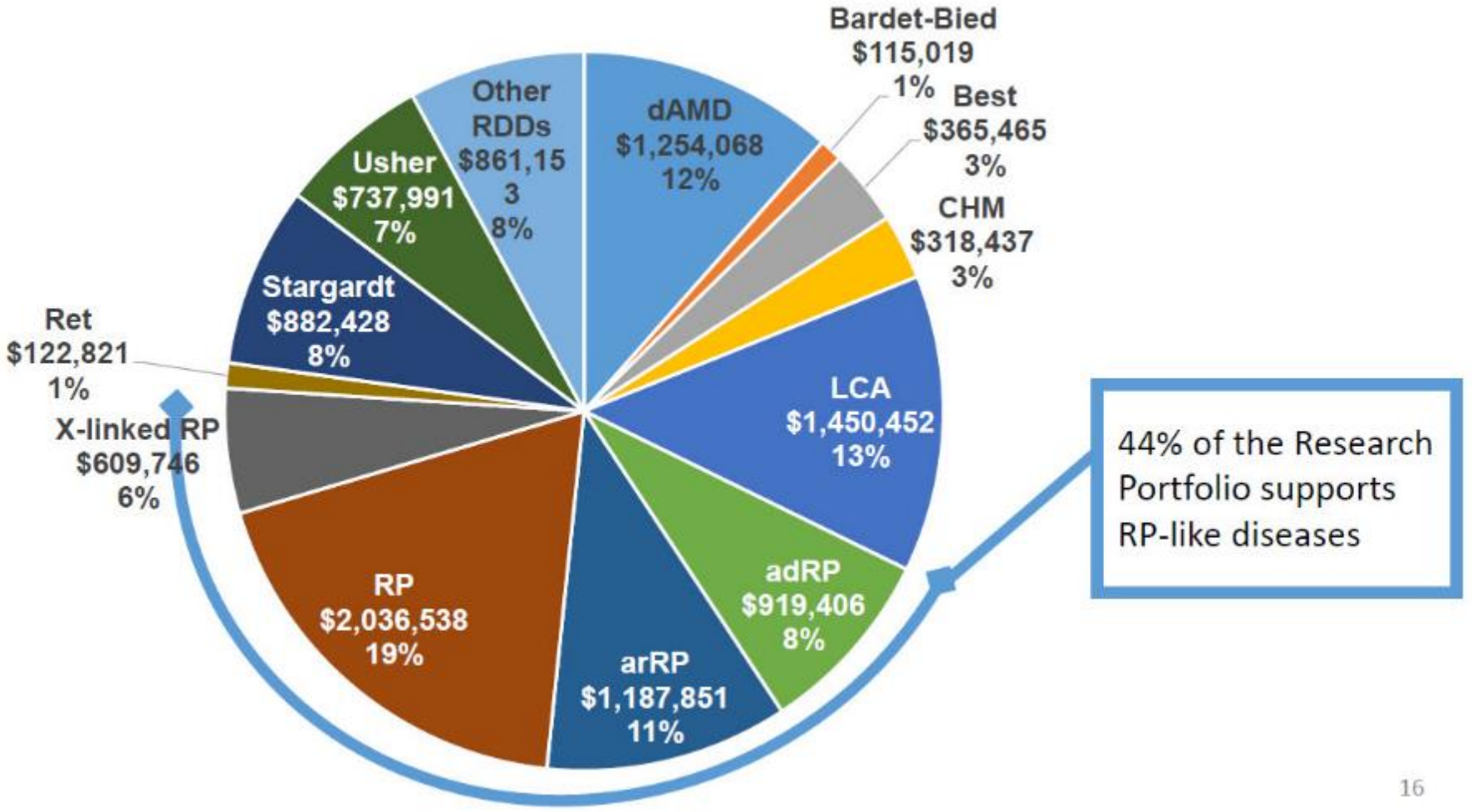


2017 Status

27 therapeutics in pre-IND and IND phase-

27 ongoing clinical trials in iRD

FY16 Research by Disease



FOUNDATION FIGHTING BLINDNESS

FFB Support Underlies Numerous Research and Discovery Successes

- Discovery of the first gene mutation causing an RDD (1989)
- Discovery of 90% of the genes implicated to date in RDD
- Identification of CFH gene (50% of all AMD)
- First successful retinal cell transplantation in animals (1988)
- Demonstration that Vitamin A can slow vision loss in retinitis pigmentosa
- The Argus II artificial retina – early development supported by FFB
- Neurotech Encapsulated Cell Technology (ECT) to deliver proteins to retina
- Stem cells successfully differentiated into retinal cells (2009, Tom Reh)
- Development of retinal cells from skin cells (Clegg, Gamm, Stone)
- ACT clinical trial in at UCLA, Moorfields Eye Hospital
  - 30 years support Ray Lund

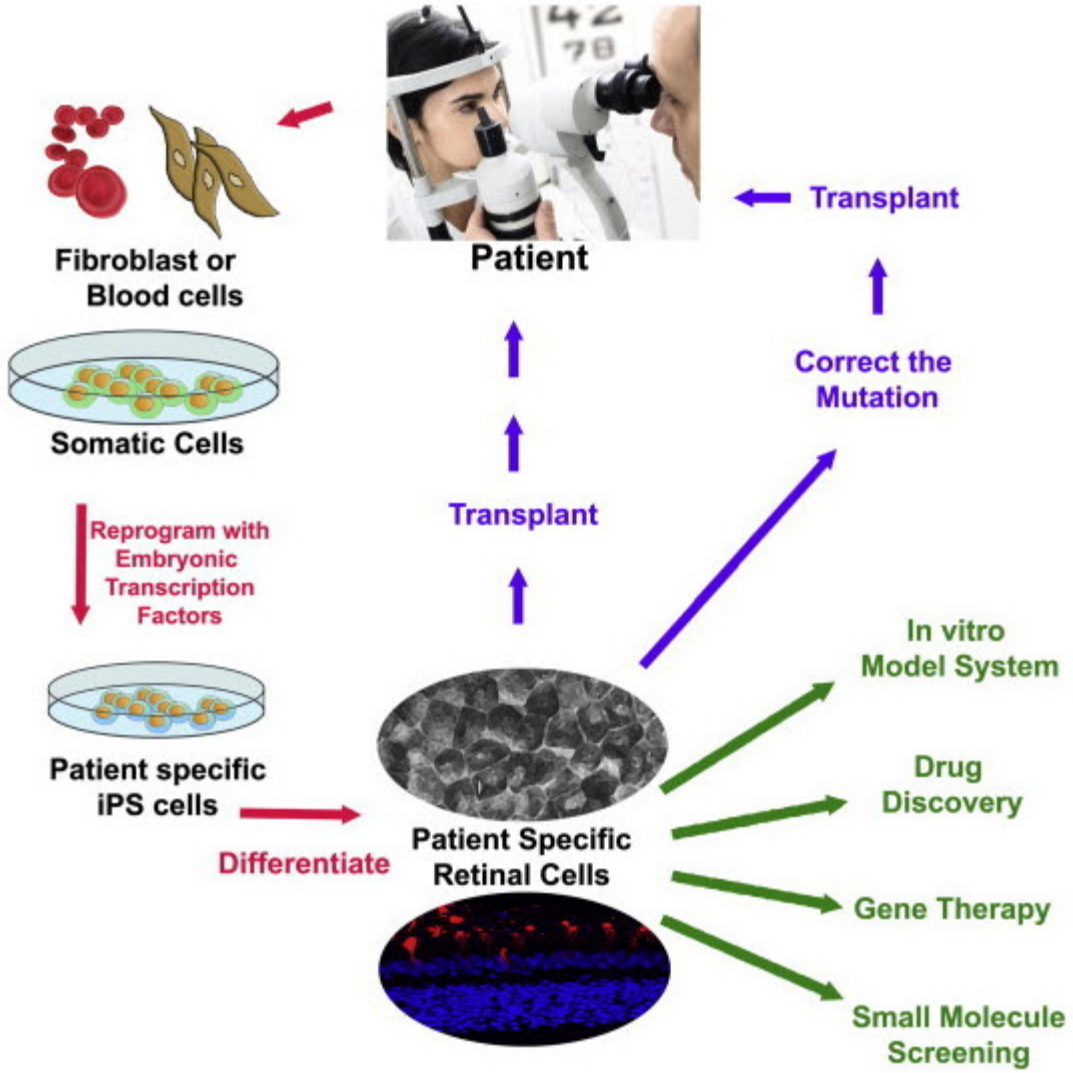
FOUNDATION FIGHTING BLINDNESS

FFB Support Underlies Translation Into Clinical Trials

- Gene therapy for LCA2
- CNTF protein therapy for RP, AMD
- DHA (docosahexanoic acid) for XLRP
- DHA + Vitamin A for RP
- Valproic acid for ADRP
- StarGen™ gene therapy for Stargardt's Disease
- Differentiated stem cell transplantation for Stargardt's Disease, AMD
- UshStat™ gene therapy for Usher 1b syndrome
- ReNeuron
- jCyte

Usher 2A: Syndromic and Non-syndromic

- Usher 2A gene encodes Usherin, a 575.6 Kd protein in the connecting ciliary body of the photoreceptors and in sensory hair cells of the cochlea, it is associated transiently with the hair bundles during postnatal development.
- Ush2A gene responsible for highest %age of recessive retinitis pigmentosa without deafness.
- Genetically heterogeneous autosomal recessive disorder characterized by sensorineural hearing deficiencies at birth and later development of progressive retinitis pigmentosa (RP).
- Most frequent cause of combined deafness and blindness in adults and affects 3 to 6% of children born with hearing impairment.
- Mutations can cause truncated Usherin and Usherin with the wrong amino acid inserted- in both cases the Usherin protein does not function and retinal degeneration occurs (and in syndromic Usher 2A, hearing loss from birth or shortly thereafter ensues).



- Optic Cups have been used to validate gene therapy for a FDA authorized clinical trial
- Optic Cups have been used as pre-clinical proof of biological effect for small molecule drugs and biologics
- Since Optic Cups can be made from iPSC from individuals with different gene mutations, they can be used to determine the effectiveness of a potential treatment across multiple iRDs

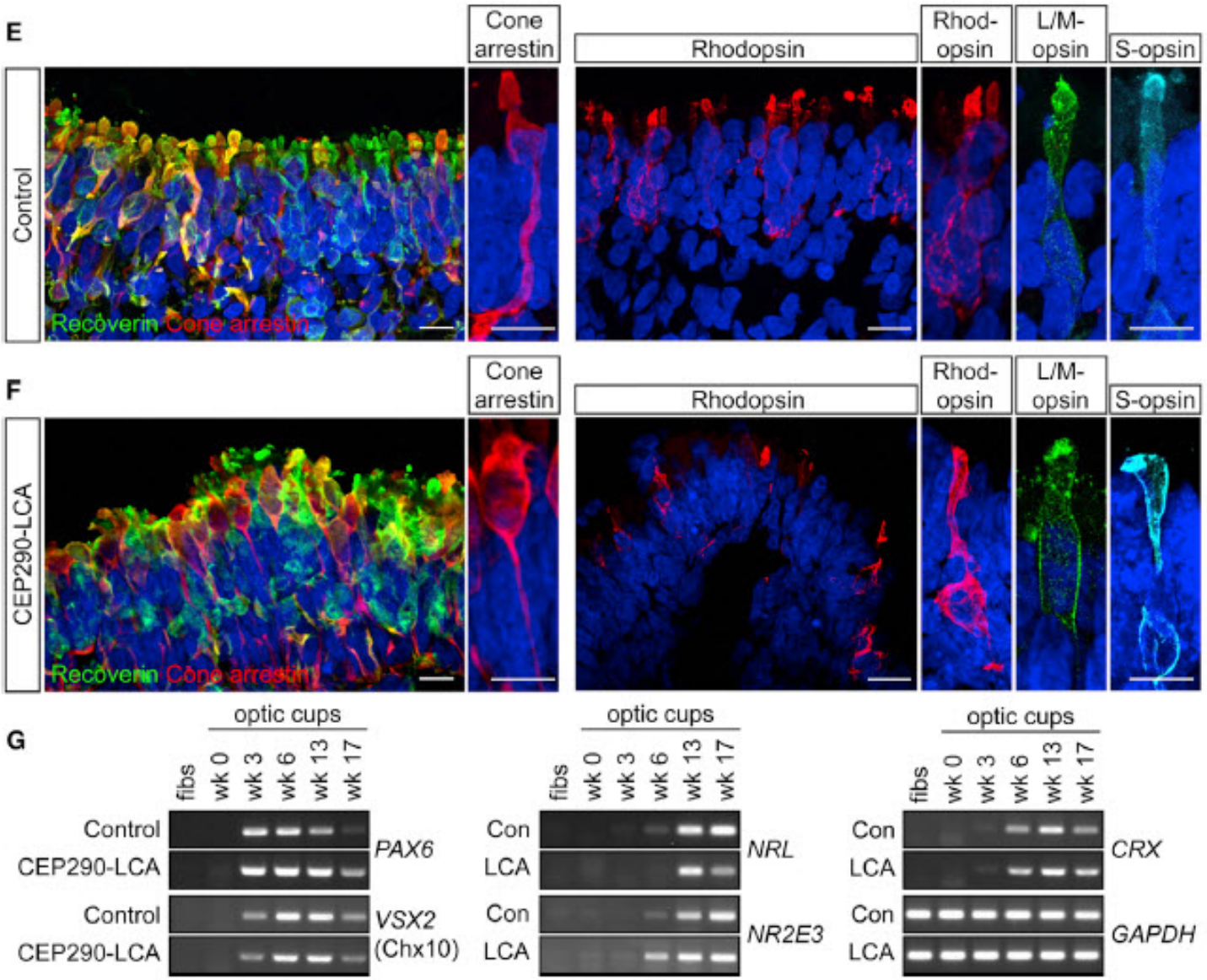


Figure 3. Generation of Opsin-Expressing Photoreceptors from iPSC Optic Cups following Long-Term 3D Suspension Culture

(A) Schematic of differentiation process from iPSCs to photoreceptor cells based on previously described method for the generation of optic cups from human embryonic stem cells (Nakano et al., 2012).

SUMMARY

Leber congenital amaurosis (LCA) is an inherited retinal dystrophy that causes childhood blindness. Photoreceptors are especially sensitive to an intronic mutation in the cilia-related gene CEP290, which causes missplicing and premature termination, but the basis of this sensitivity is unclear. Here, we generated differentiated photoreceptors in three-dimensional optic cups and retinal pigment epithelium (RPE) from iPSCs with this common CEP290 mutation to investigate disease mechanisms and evaluate candidate therapies. iPSCs differentiated normally into RPE and optic cups, despite abnormal CEP290 splicing and cilia defects. The highest levels of aberrant splicing and cilia defects were observed in optic cups, explaining the retinal-specific manifestation of this CEP290 mutation. Treating optic cups with an antisense morpholino effectively blocked aberrant splicing and restored expression of full-length CEP290, restoring normal cilia-based protein trafficking. These results provide a mechanistic understanding of the retina-specific phenotypes in CEP290 LCA patients and potential strategies for therapeutic intervention.

Challenges Specific To Gene And Cell Therapies

Novel technologies/pathways are being developed, and addressing untapped orphan blindness indications

- New approaches such as gene therapy, gene editing, new Mab targets and RNA editing have the potential to create value in monogenic and underserved blindness disorders, such as Leber's Congenital Amaurosis (LCA)
- Gene therapy development is more complex. Need to understand safety of virus, construct, promotors, target cells
- No approvals of cell or gene therapy yet for any iRD
- Gene editing (CRISPR-Cas9) *in vivo* / *in situ* still a ways off – off target changes have to be addressed
- Sub-retinal administration is complex, not well standardized and cannot be left to non-trained ophthalmologists
- Access to GMP manufacturing facilities for vector production and cell productions

Importance Of Validation Of New Clinical Endpoints

VALIDATED FUNCTIONAL (VISION) ENDPOINTS CAN DE-RISK RETINAL DRUG DEVELOPMENT

Clear, achievable endpoints are a necessary requisite for successful drug development in any area of medicine, and many retinal diseases are well positioned in this regard

FDA has stated that it will consider improvements in functional and/or anatomical endpoints from adequate and well-controlled studies that use well-defined and reliable methods of assessment, to provide substantial evidence that natural history has been altered for patients with a retinal disease

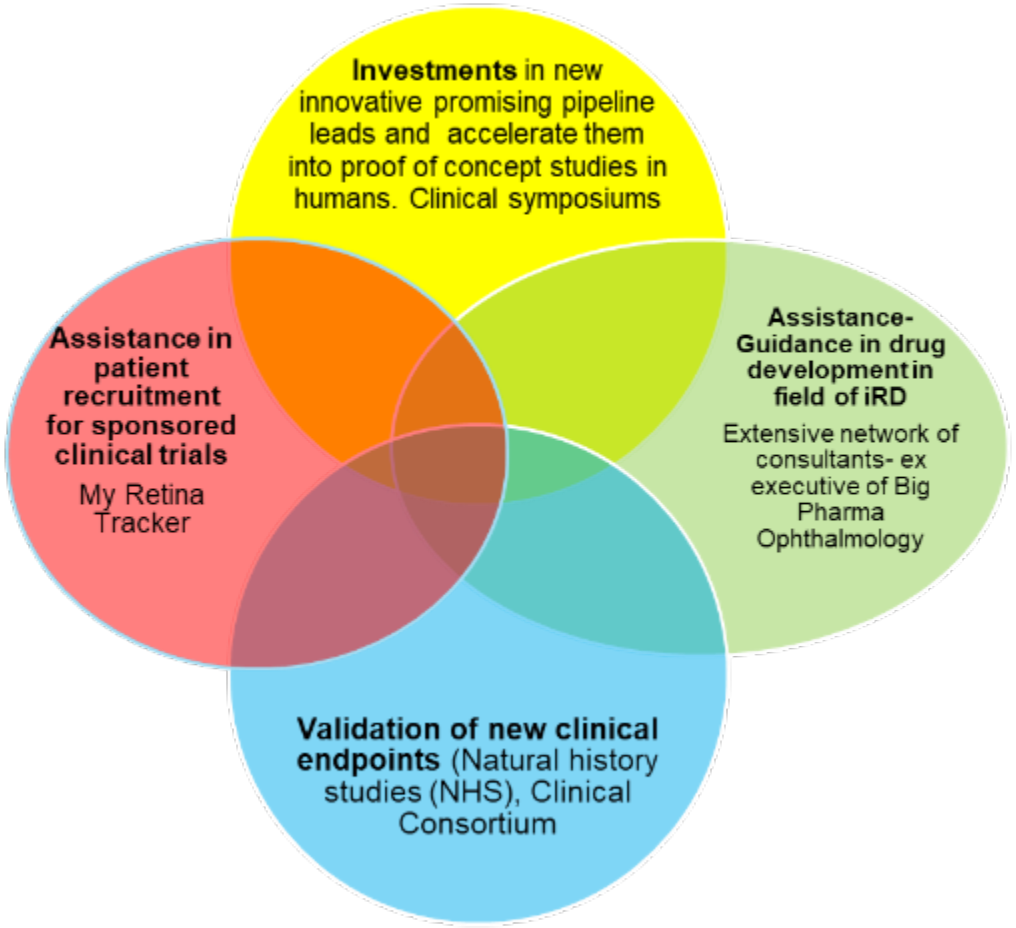
OBJECTIVE ANATOMIC ENDPOINTS CAN OFFER ALTERNATIVES TO FUNCTIONAL (VISION) ENDPOINTS

The availability of robust diagnostic/imaging technology allows retinal specialists to clearly determine the outcome of treatment for inherited rare retinal degenerations (e.g. - SD OCT and EZ Area). FDA accepted structural endpoint for registration.

The technology also provides essential information for investors to assess the probability of clinical success for new agents based on the correlation between functional (visual acuity) and structural/anatomic (retinal morphology) responses to treatment

FOUNDATION FIGHTING BLINDNESS

FFB Clinical Research Institute – Four Key Focus



FOUNDATION FIGHTING BLINDNESS

Validation of New Clinical Endpoints

Validation of new clinical endpoints – more sensitive and more reproducible – has been identified as a priority for FFB CRI, to help better design clinical trials and to attract development of therapeutics for RDDs

Approach through:

- Natural history studies, (ProgSTAR, RUSH2A)
- Ongoing clinical trials funded by FFB or FFB CRI
  - (Validation of “EZ area” as a clinical endpoint for retinitis pigmentosa)

ProgStar: The International Study of Stargardt's Disease

progstar.org

Project Description and Objective → "What"	
1	ProgSTAR1 evaluates the natural history of Stargardt's Disease (ABCA4) in a **retrospective** cohort with 251 patients
2	ProgSTAR2 evaluates the natural history of Stargardt's Disease (ABCA4) in a **prospective** cohort with 259 patients for 2 years a. SMART is a subset of ProgSTAR2 to evaluate Scotopic Microperimetric Assessment of Rod Function in Stargardt's Disease with133 patients
3	ProgSTAR4 evaluates the natural history of Stargardt's Disease in a prospective cohort of patients with the rare PROM1 gene mutation; funding is from Shulsky Foundation

Project Rationale→ "Why"
• Determine best outcome measures to accelerate evaluation of emerging treatments for Stargardt's Disease
• Better understand Stargardt's Disease progression for selecting future clinical trial participants
• Identify potential participants for forthcoming clinical trials

FFB CRI Clinical Consortium

Mission Statement

To accelerate the development of treatments for inherited retinal diseases (IRDs) through collaborative and transparent clinical research

Consortium launched in collaboration with Jaeb Center for Health Research (DRCNet)

Executive committee includes:

Drs. J. Duncan, D. Birch, R. Ferris, M. Maguire, M. Pennesi, A. Ayala, J. Cheetham, A, Glassman, P. Zilliox

A natural history study on the progression of USH2A is the first clinical study within the Consortium

Project: RUSH2A --The 1st Consortium Study

Project Description and Objective → "What"

• RUSH2A (Rate of Progression of USH2A Related Retinal Degeneration) characterizes the natural history of retinal degeneration associated with biallelic mutations in the USH2A gene over 4 years with 2 mutation cohorts
  • With congenital hearing loss (Usher syndrome type 2A)
  • Without symptomatic congenital hearing loss (Retinitis Pigmentosa (RP))

Project Rationale→ "Why"
• Attract investment for treatments of this disease • Determine best outcome measures to accelerate evaluation of emerging treatments for USH2A • Better understand USH2A progression for selecting future clinical trial participants • Identify potential participants for forthcoming clinical trials

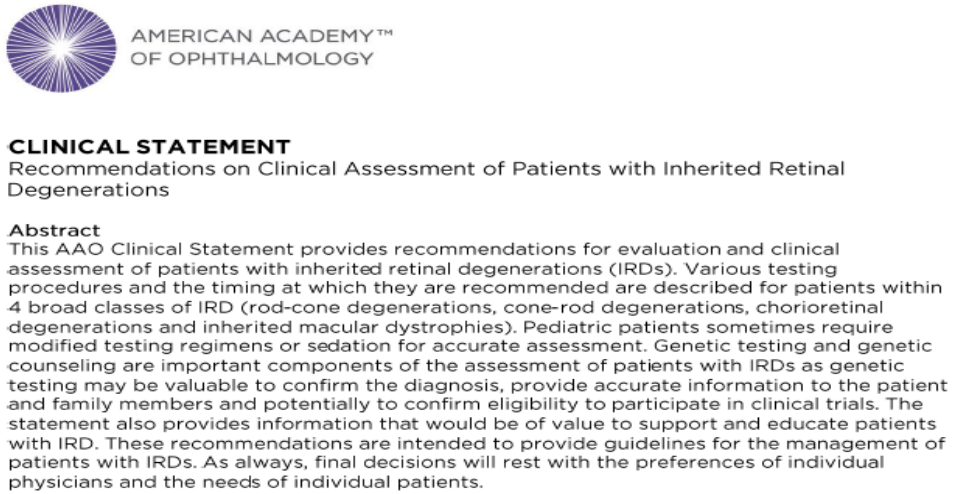
Clinical Consortium of 20+ Centers Worldwide

UCSF, San Francisco, CA
VRA, Gainesville, FL
Emory, Atlanta, GA
MEEI, Boston, MA
Michigan, Ann Arbor, MI
Wilmer, Baltimore, MD
NEI, Bethesda, MD
Duke, Raleigh-Durham, NC
Rutgers, Jersey City, NJ
Columbia, NY, NY
Cincinnati, OH
Casey, Portland, OR
Scheie, Philadelphia, PA
RFSW, Dallas, TX
Baylor, Houston, TX
Utah, Salt Lake City, UT
MCW, Milwaukee, WI
Ghent, Belgium
Sick Kids, Toronto, Canada
Moorfields, London, England
Institut de la Vision, Paris, France
Tubingen, Germany
Radboud University, Nijmegen, The Netherlands

Assistance- Guidance in Drug Development in Field of iRD

Assistance to small Biotech in drug development through

- Access to Extensive network of consultants- ex executive of Big Pharma Ophthalmology
- Works shops, Symposium



AMERICAN ACADEMY™
OF OPHTHALMOLOGY

CLINICAL STATEMENT
Recommendations on Clinical Assessment of Patients with Inherited Retinal Degenerations

Abstract
This AAO Clinical Statement provides recommendations for evaluation and clinical assessment of patients with inherited retinal degenerations (IRDs). Various testing procedures and the timing at which they are recommended are described for patients within 4 broad classes of IRD (rod-cone degenerations, cone-rod degenerations, chorioretinal degenerations and inherited macular dystrophies). Pediatric patients sometimes require modified testing regimens or sedation for accurate assessment. Genetic testing and genetic counseling are important components of the assessment of patients with IRDs as genetic testing may be valuable to confirm the diagnosis, provide accurate information to the patient and family members and potentially to confirm eligibility to participate in clinical trials. The statement also provides information that would be of value to support and educate patients with IRD. These recommendations are intended to provide guidelines for the management of patients with IRDs. As always, final decisions will rest with the preferences of individual physicians and the needs of individual patients.

FOUNDATION FIGHTING BLINDNESS

MY RETINA TRACKER™

Track Your Vision. **Drive the Research.**

Updated and expanded online version of the Foundation's disease registry for people with inherited retinal diseases, available at www.MyRetinaTracker.org

Mission: Enable people with inherited, degenerative orphan retinal diseases, their doctors and researchers to actively collaborate in the research process. This will be accomplished by:

- Patients sharing information about the history, progression and personal impact of their disease
- Patients authorizing their doctors to share their diagnosis, and select current and future clinical information
- Patients participating in research studies when they are identified by researchers as potentially good subjects for their studies and contacted through My Retina Tracker ™.

Designed with state-of-the-art database technology to protect participant privacy and ensure ease of use

SUMMARY

- Anti-sense RNA oligonucleotides are a viable treatment strategy for inherited rare retinal degenerations
- Proof of concept using anti-sense oligos has shown in multiple iRD models
- Optic Cups from individuals with the iRDs are being used to bridge from animal models to human iRD specific conditions
- FFB's RUSH2A natural history study provides information needed to determine timing of treatment and EZ Area is a FDA accepted endpoint for the retinal degeneration seen in Usher 2A syndromic and non-syndromic retinal degeneration.
- FFB Clinical Consortium could provide validated and qualified clinical centers to conduct a clinical trial.

Thank you

Visit
www.fightblindness.org

QR-313 for Dystrophic Epidermolysis Bullosa

Presenter: **Dave Rodman**

Dystrophic Epidermolysis Bullosa (DEB)

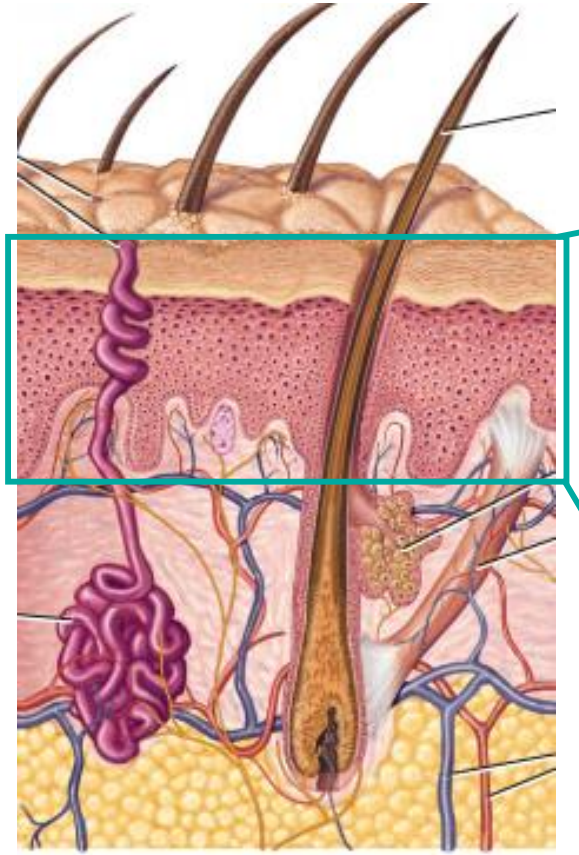
1. What is DEB and why do we think ProQR can make a difference?
2. What scientific progress have we made?
3. Where do we go from here?

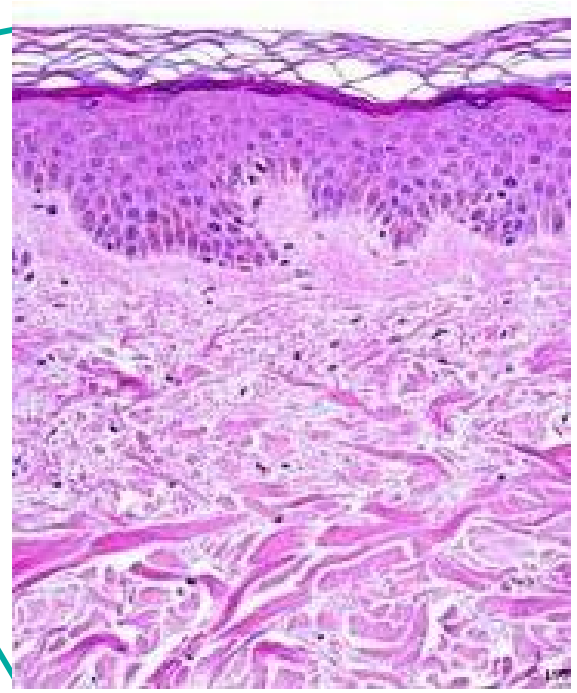
1. What is DEB

High unmet need, inadequate treatment options, good understanding of the underlying genetics and molecular pathogenesis.

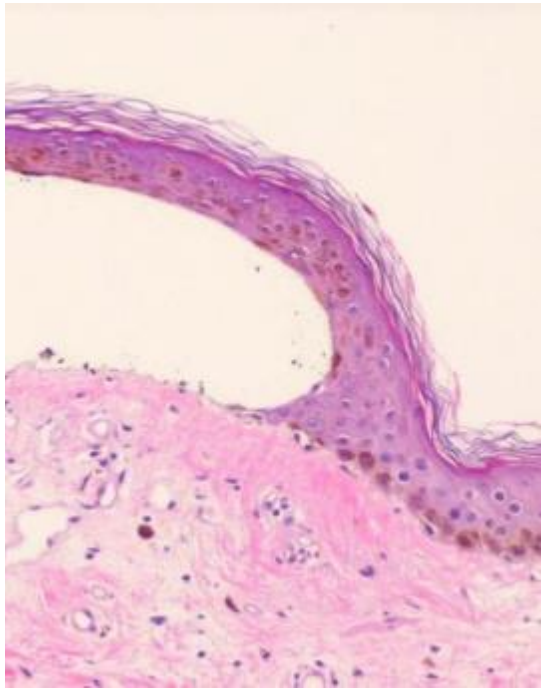
DEB pathogenesis

Histology





Healthy skin

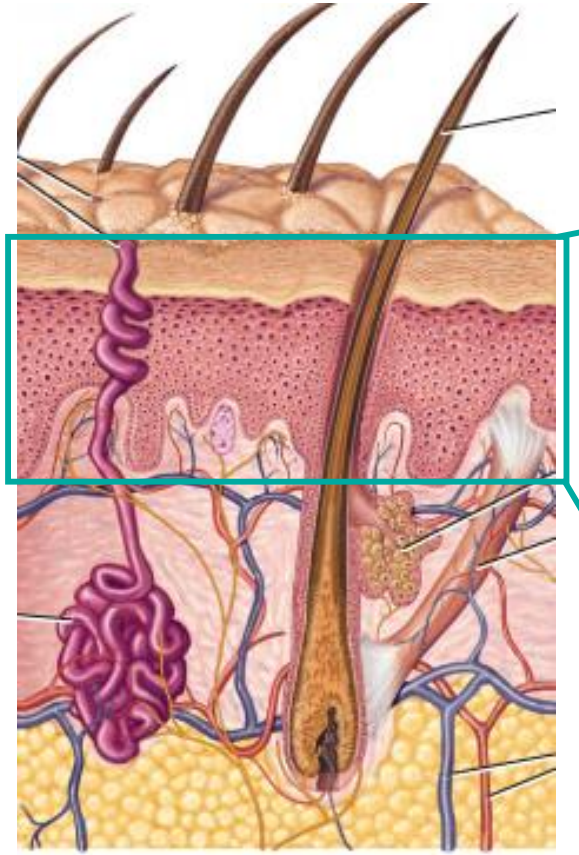


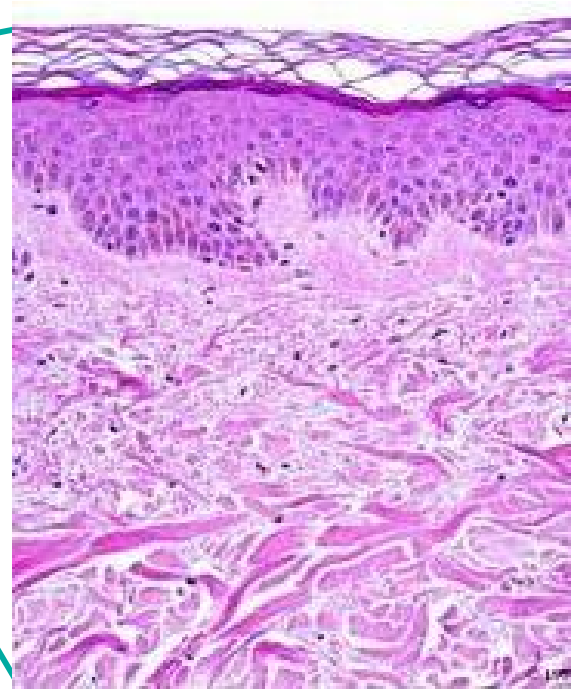
DEB skin

Skin blistering
Wound healing impaired
Infections

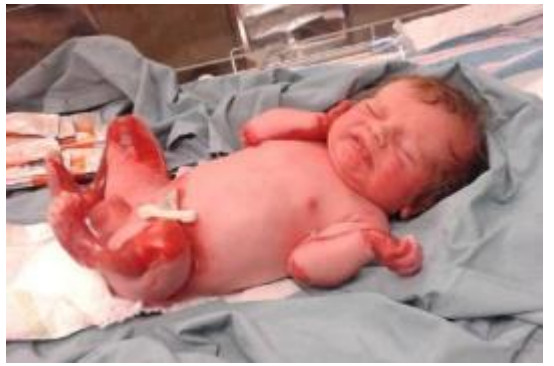
DEB pathogenesis

Histology





Healthy skin

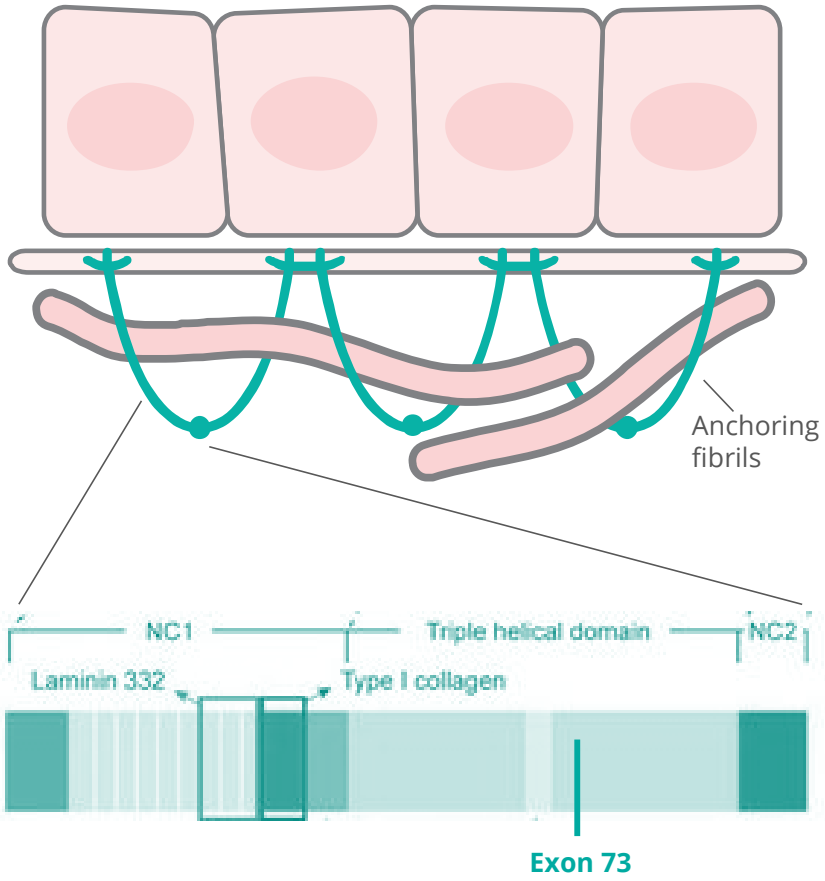


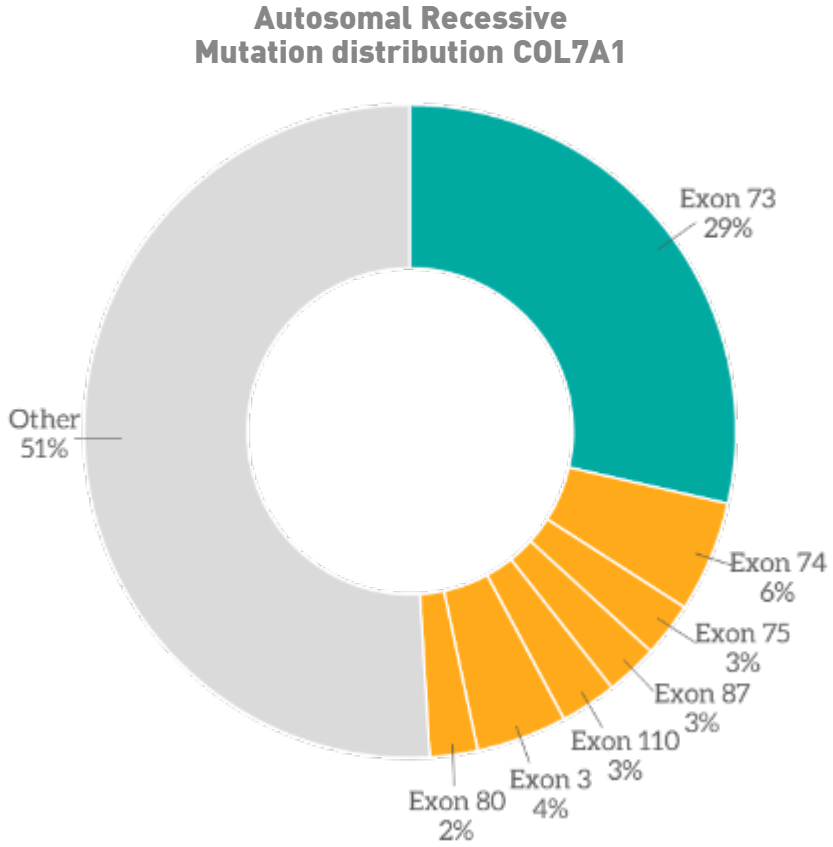
DEB skin

Skin blistering
Wound healing impaired
Infections

DEB genetics

COL7A1 encodes for the Collagen type VII (C7) protein

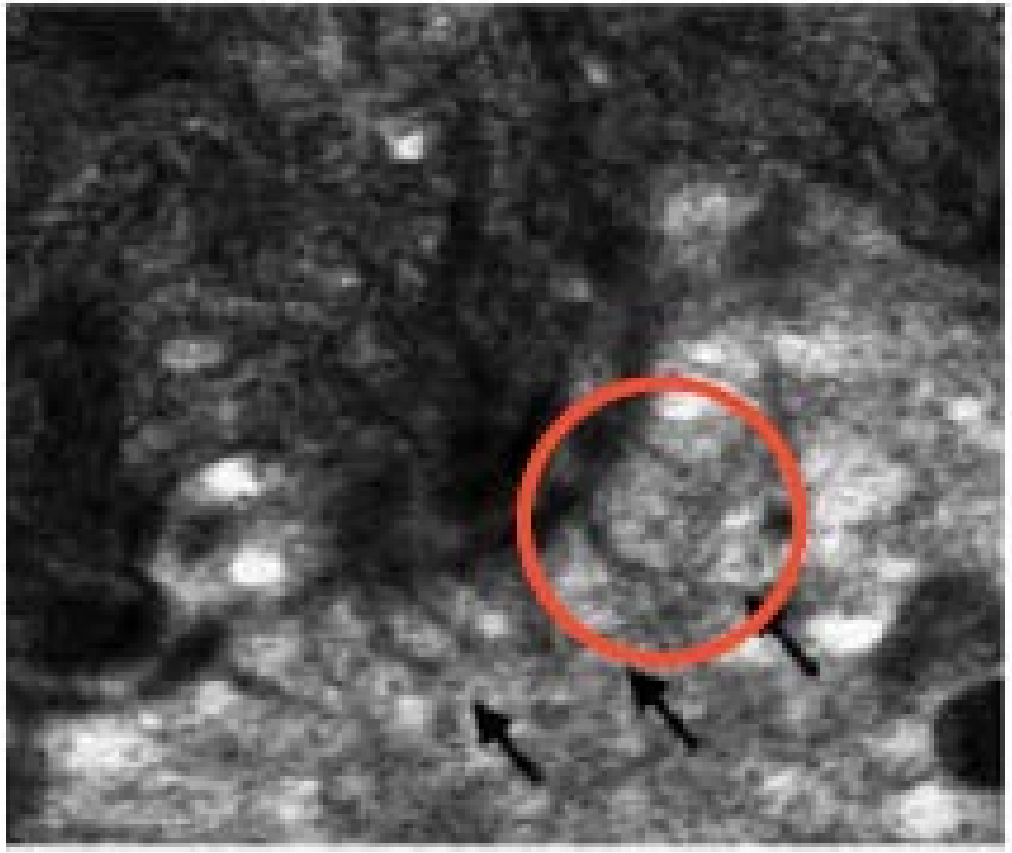


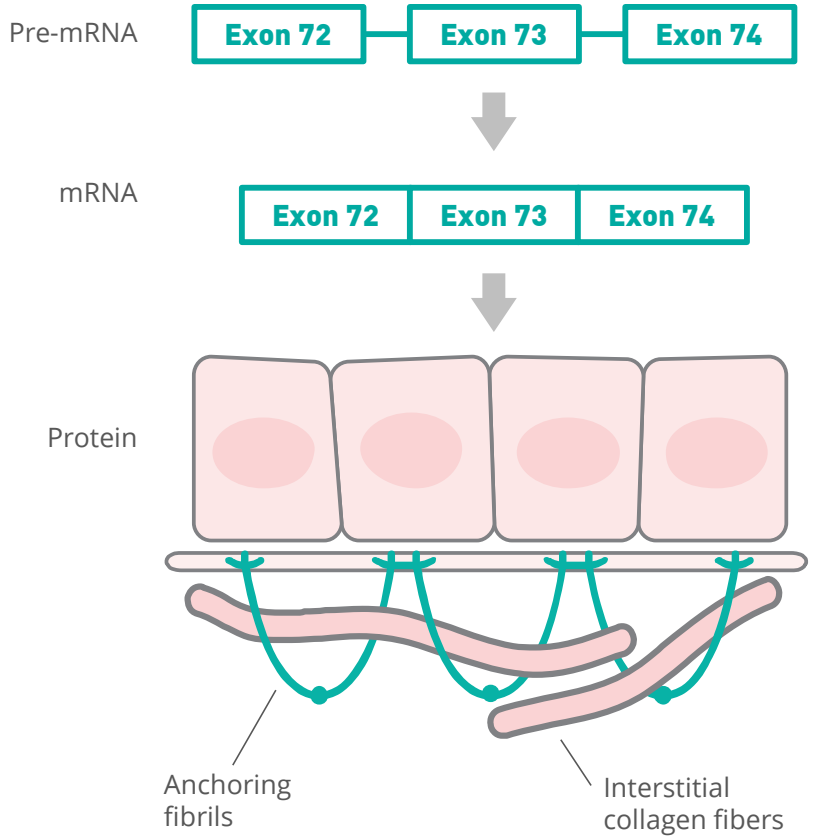


COL7A1 mutation database/Browne et al, 2011

DEB Molecular Pathogenesis

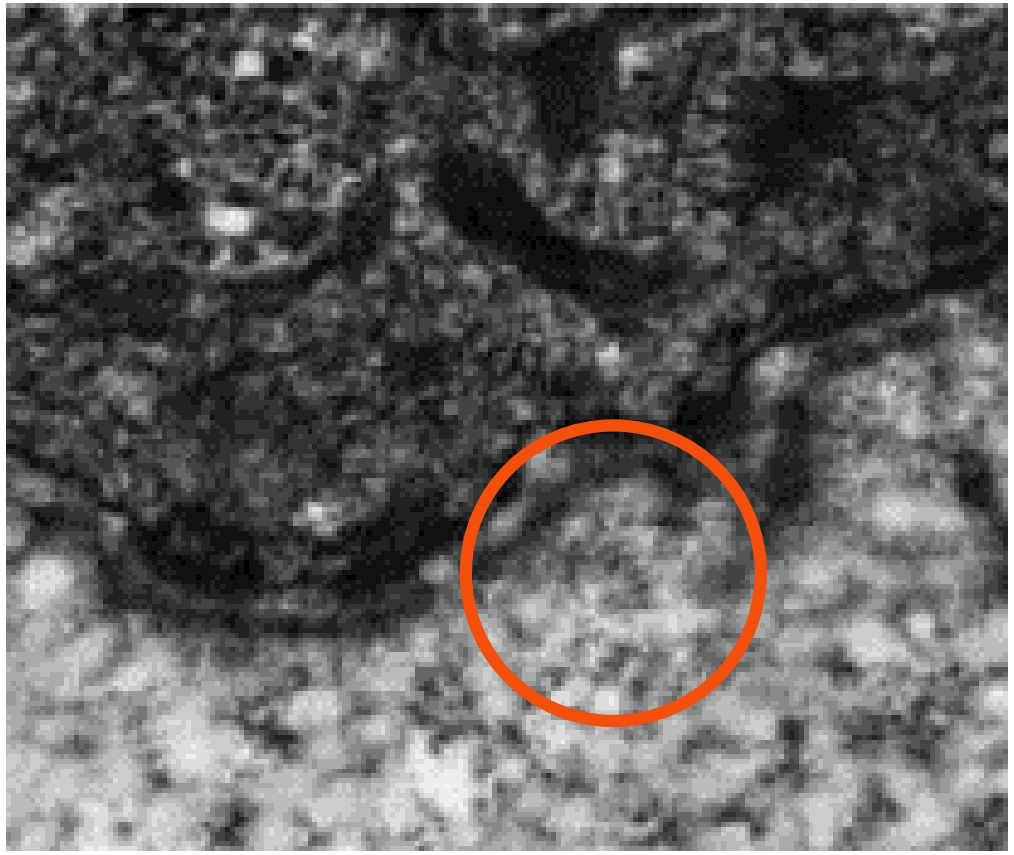
Normal formation of anchoring fibrils- no mutations in COL7A1

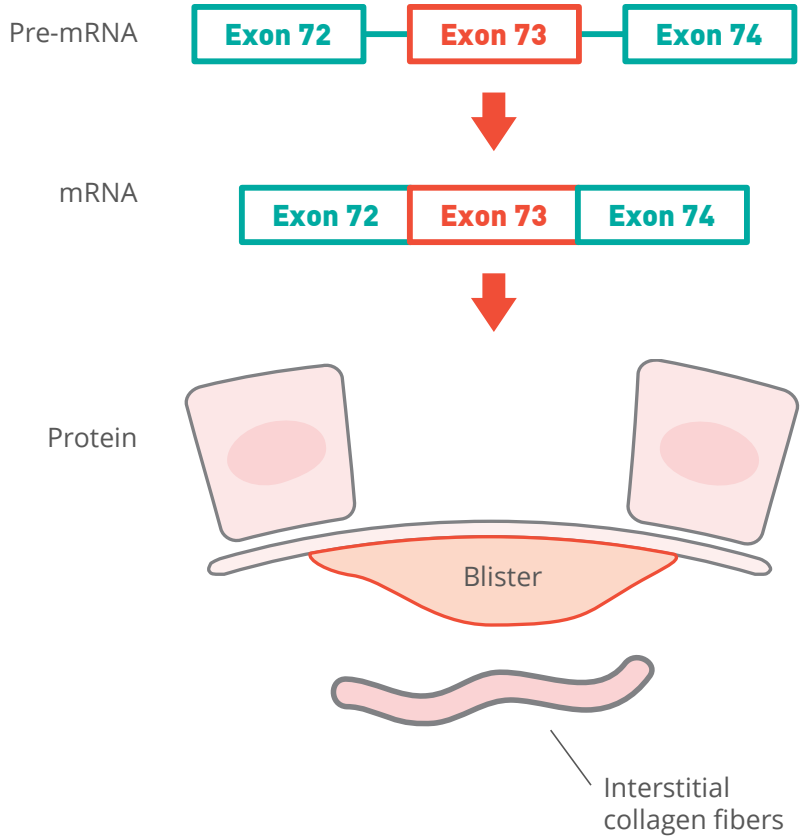




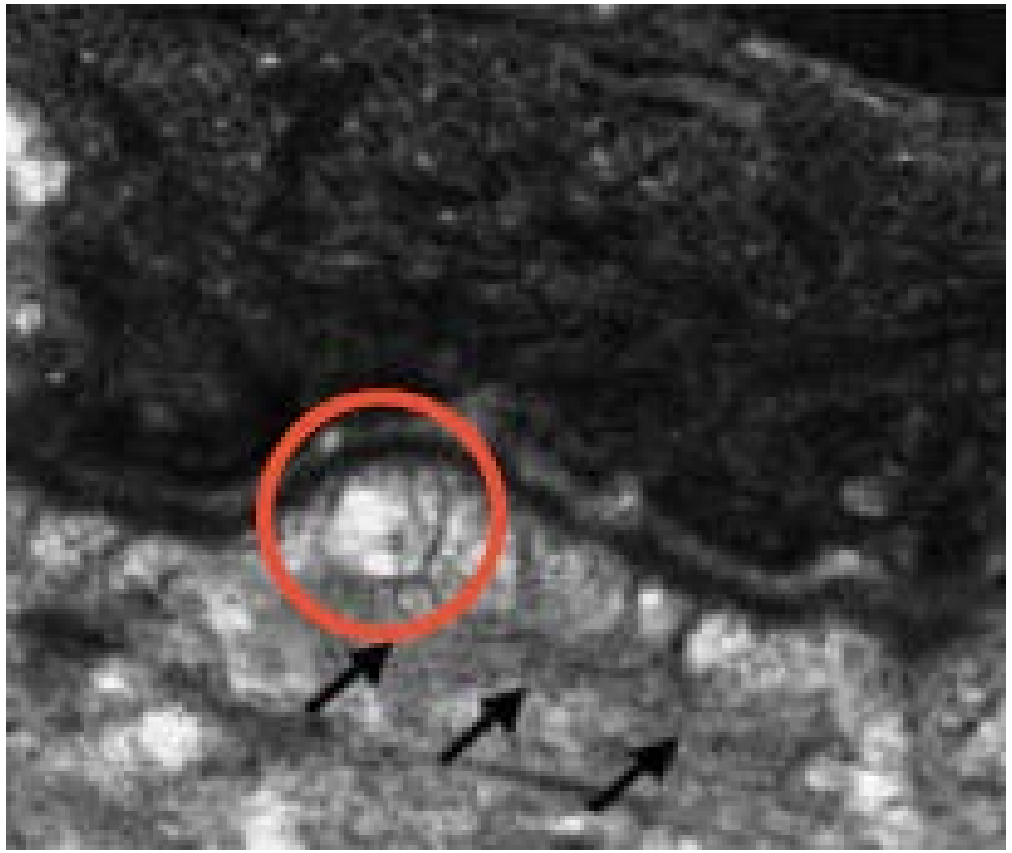
DEB Molecular Pathogenesis

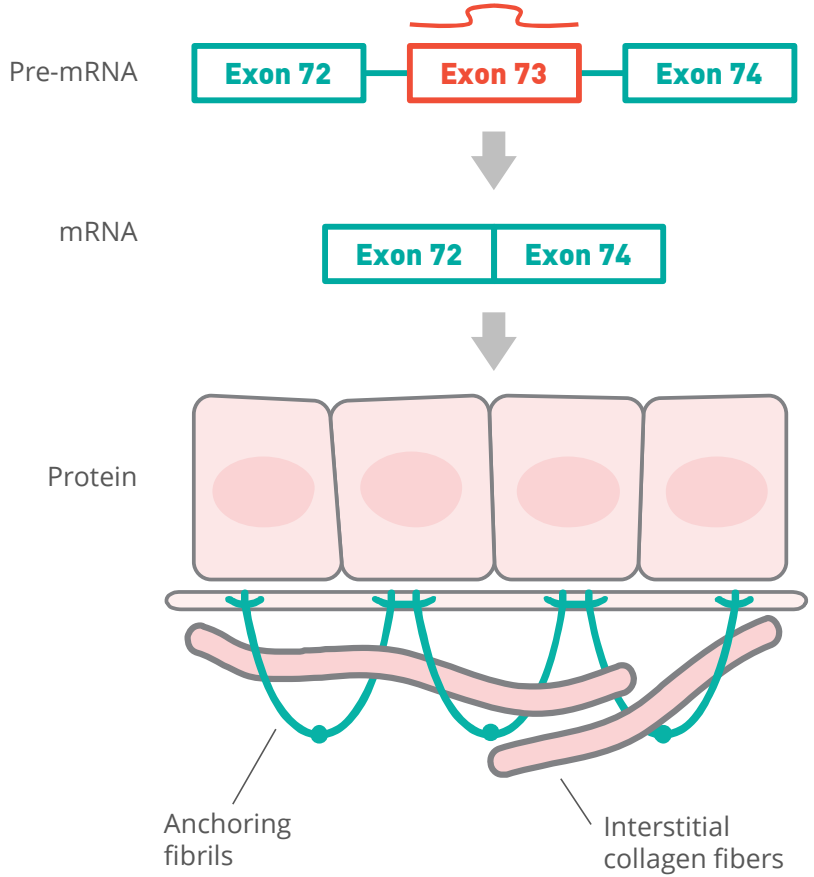
Mutations in COL7A1 lead to absence of anchoring fibrils





DEB – How can ProQR oligonucleotide therapies make a difference?





QR-313 for dystrophic epidermolysis bullosa

MOLECULAR TARGETING WITH DISEASE-MODIFICATION DUE TO LONG PROTEIN HALF-LIFE

AIMS TO HEAL WOUNDS, RESTORE SKIN AND IMPROVE QUALITY OF LIFE

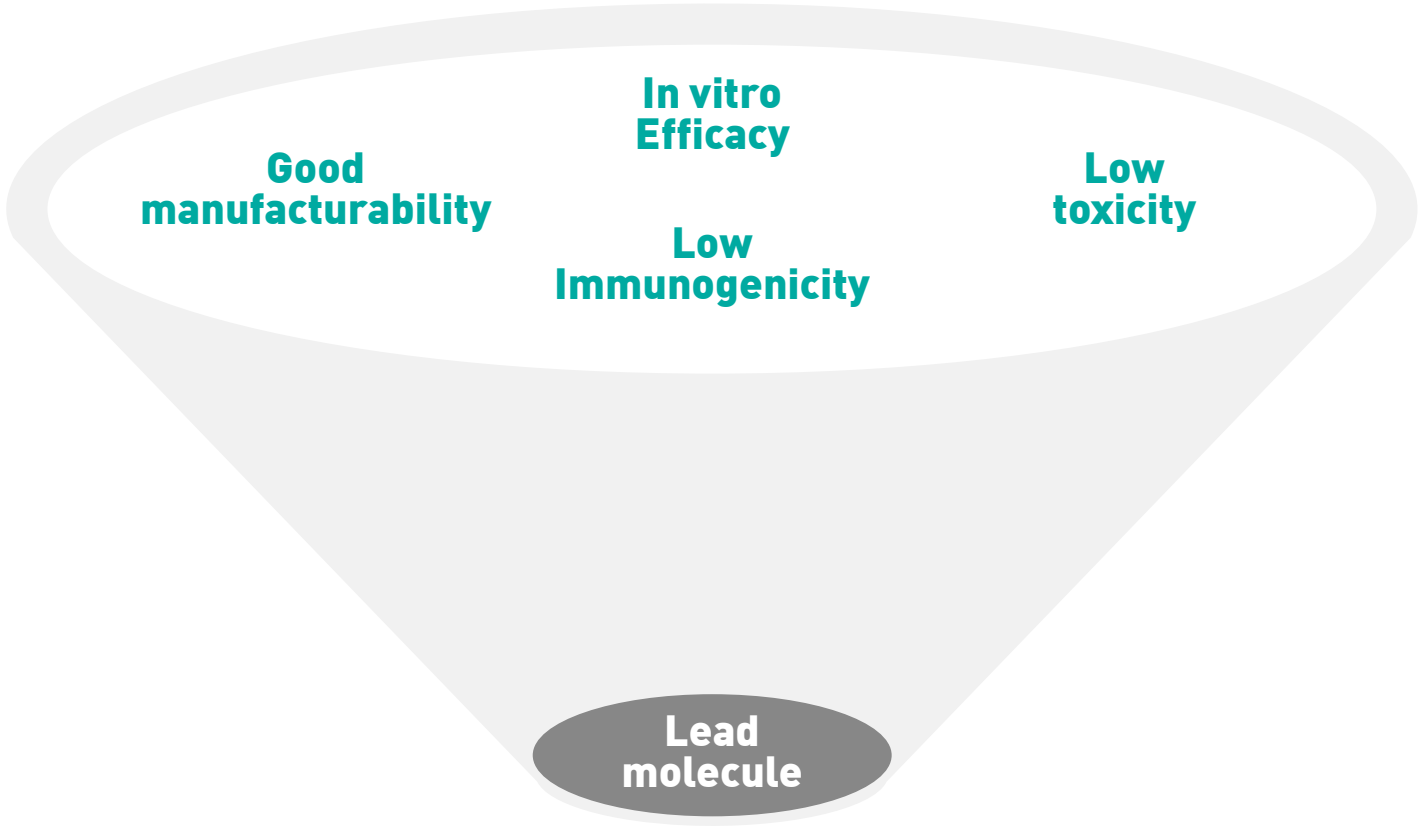
TOPICALLY APPLIED
Commonly used hydrogel, containing QR-313 RNA therapy

CONVENIENT APPLICATION AT HOME
Maximum frequency every other day

2. QR-313 Progress to date

Screen for skipping of exon 73 from COL7A1

Antisense-oligonucleotide (AON) lead selection

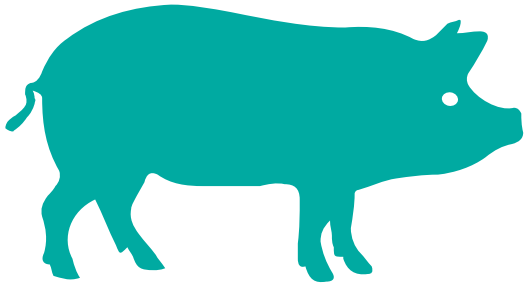


42 AONs

QR-313

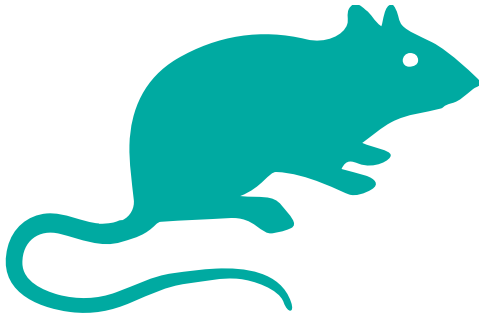
Functional characterization

Ex vivo
Human skin
equivalent model



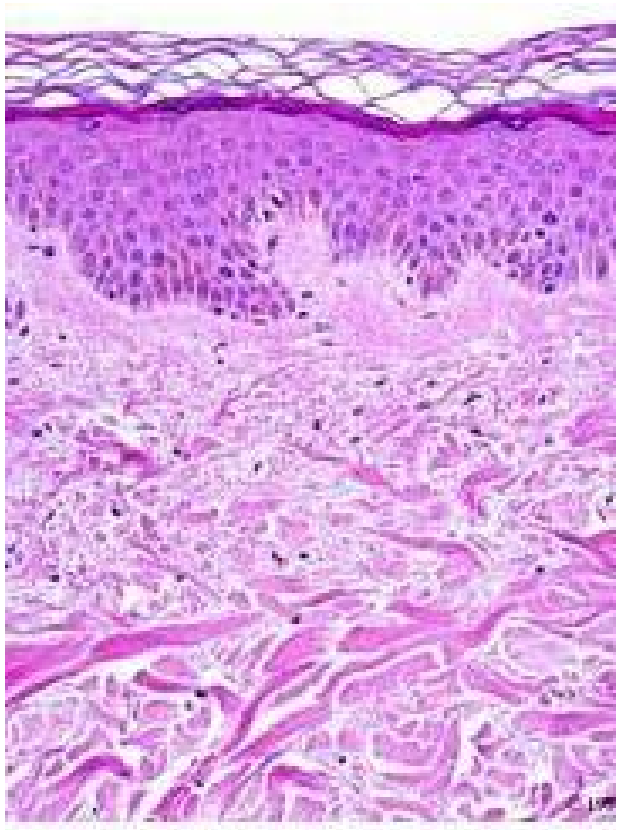
In vivo
Mini-pig dermatome
epidermal wound

Ex vivo
Human lymphocyte
T-cell activation assay

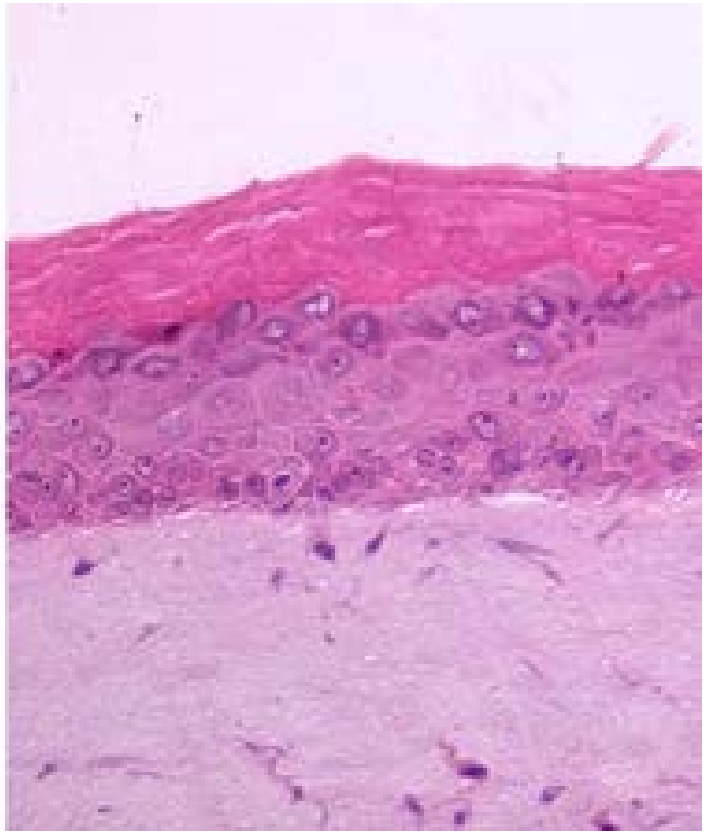


In vivo
Mouse intradermal
injection

Human skin equivalents (HSE) are highly similar to human skin



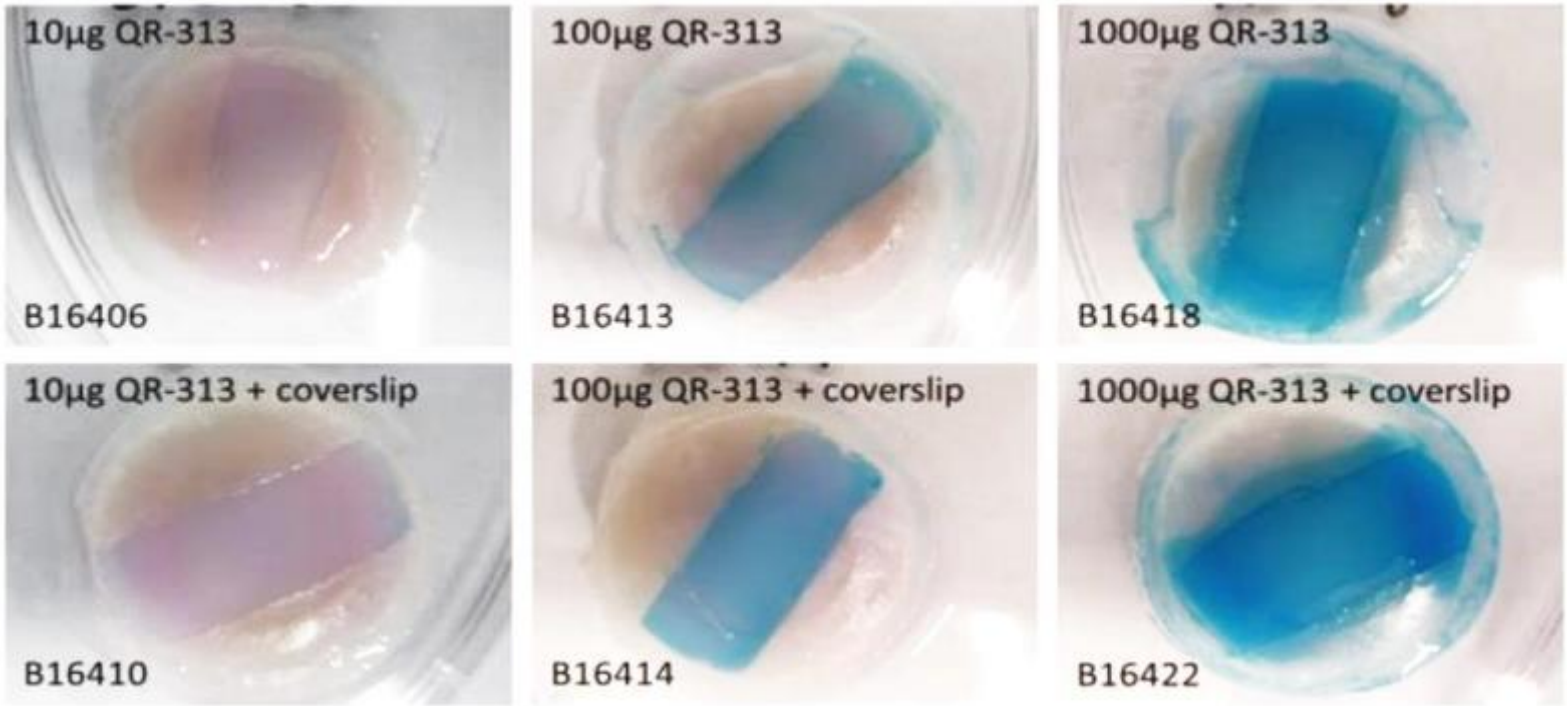
Human skin



Skin model

Macroscopic overview HSE

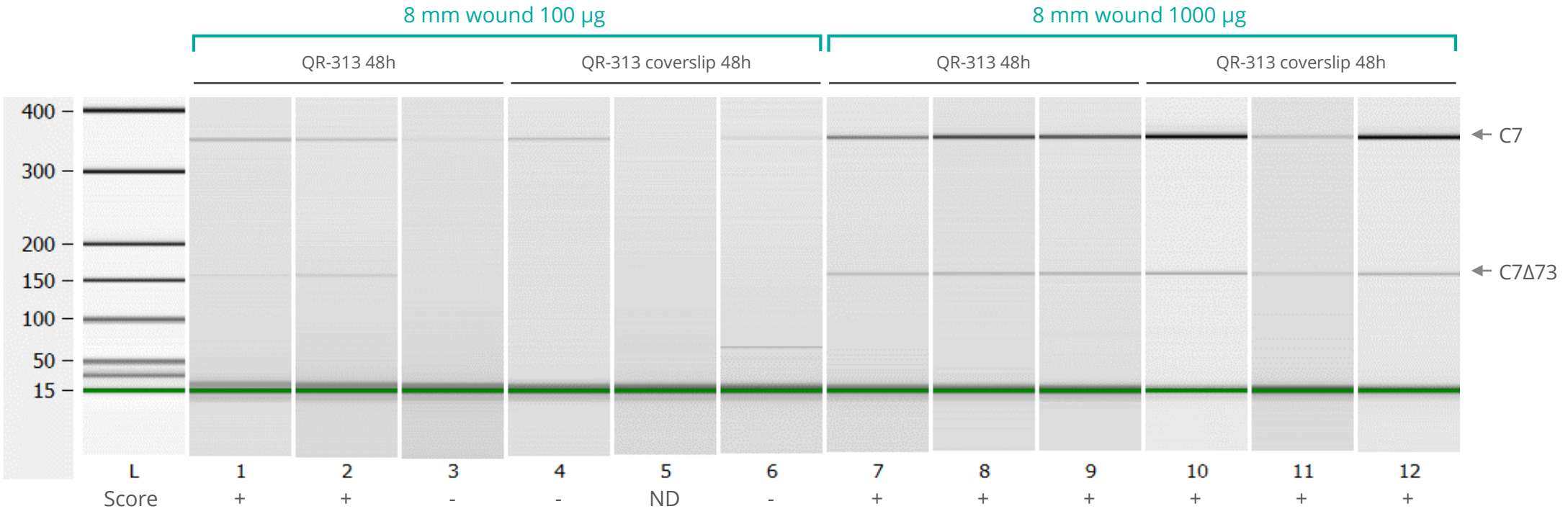
Wounded and treated with QR-313 in hydrogel



QR-313 gel is blue due to the presence of a Cy5 label on QR-313

Exon skip analyses

Example: Dermal samples – 100 and 1000 µg – 48 hours

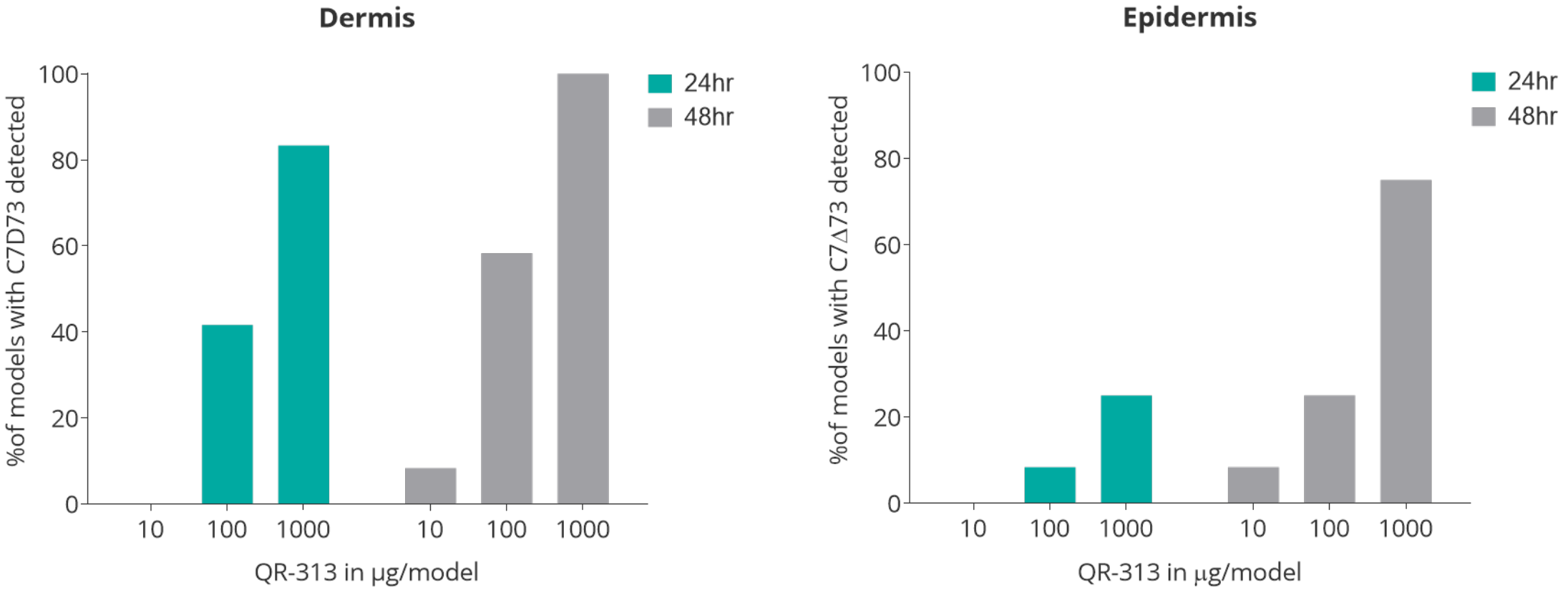


ND= no C7 detected, no analysis possible

- **100 µg QR-313**: 2/5 samples demonstrate skip = **40%**
- **1000 µg QR-313**: 6/6 samples demonstrate skip = **100%**

Summary RNA data

N=2 different donors; 6 repeats per donor

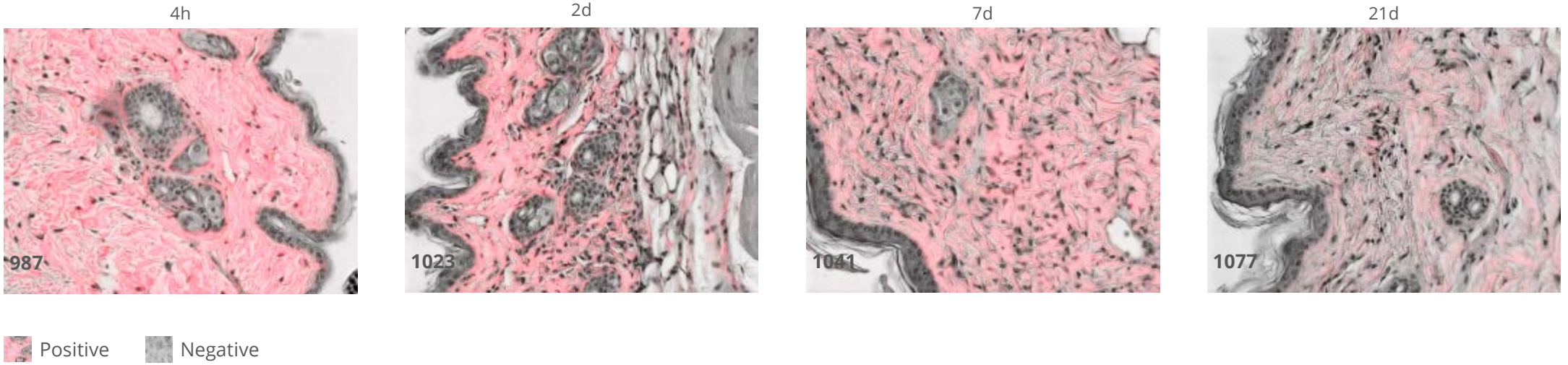


Data represented as mean of 2 donors

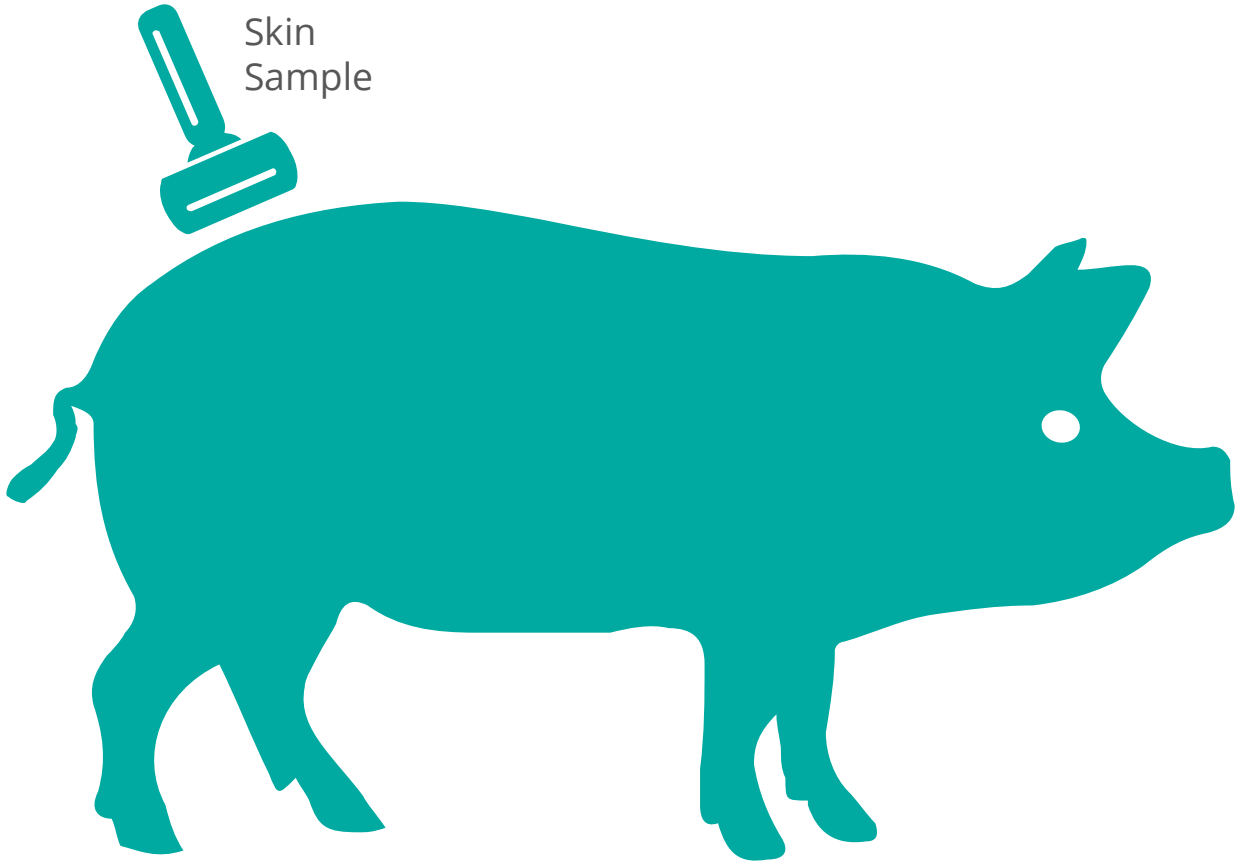
Bio distribution of QR-313 and QR-313-Cy5 after a single intradermal injection

Bio distribution of QR-313 and QR-313-Cy5 after a single intradermal injection

Local-skin

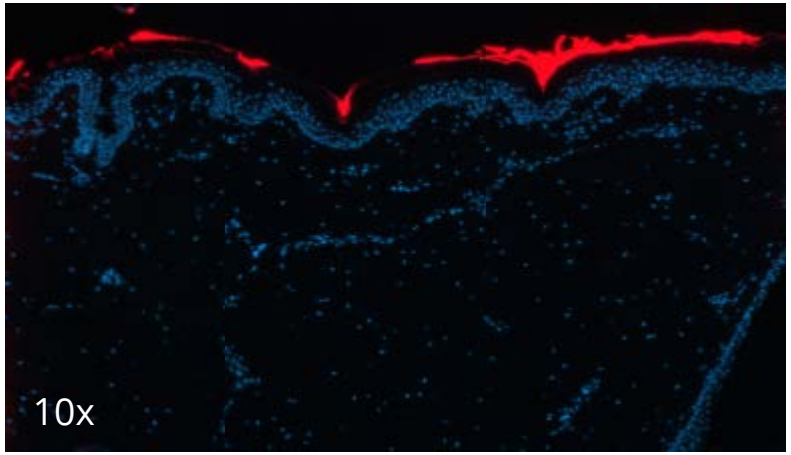


Göttingen minipig model of human wounding



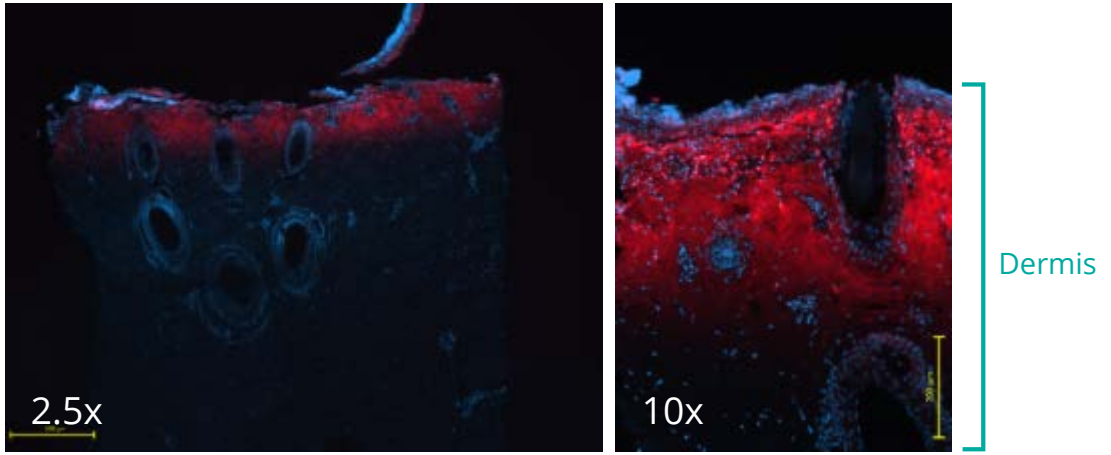
Delivery in vivo

QR-313 hydrogel applied to wounds on minipigs

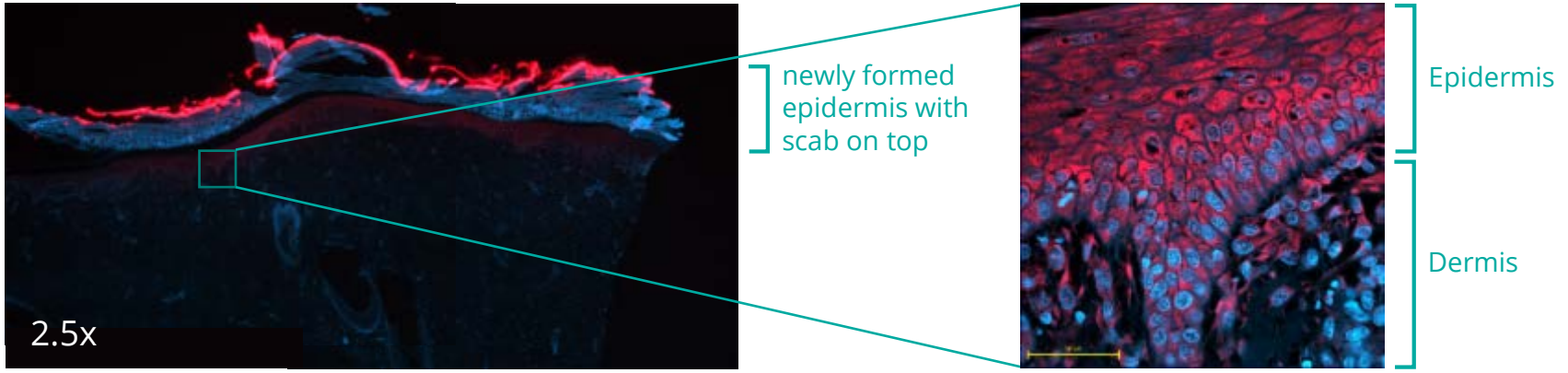


Intact skin

QR-313 Nuclei



Wounded skin 2d

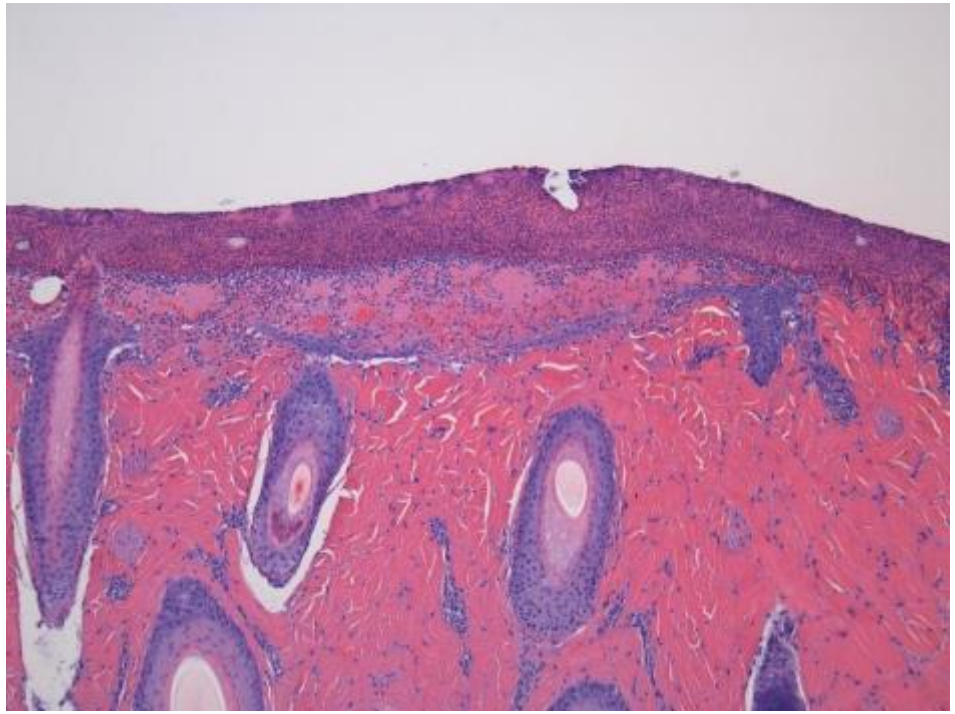


Wounded skin 7d

Tolerability in vivo

Local tolerability tested in wounded minipigs

- Histopathological examination revealed no test item related changes in sites that were not subjected to wounding.
- Wounded sites showed normal variations that were consistent with the healing process in all groups irrespective of dose.



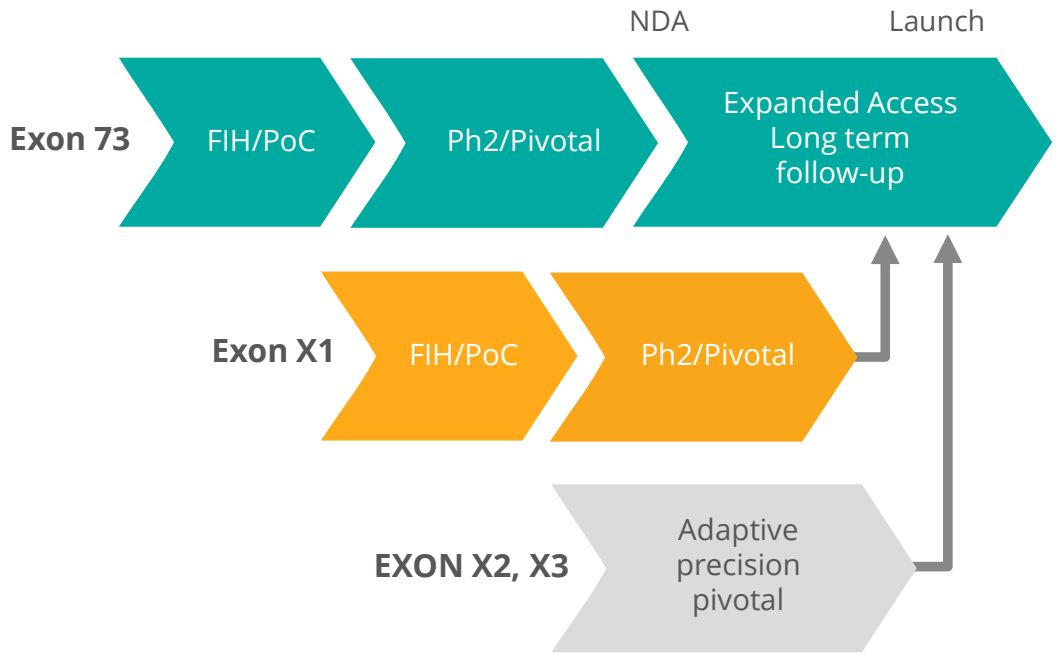
Summary of Pre-clinical Program

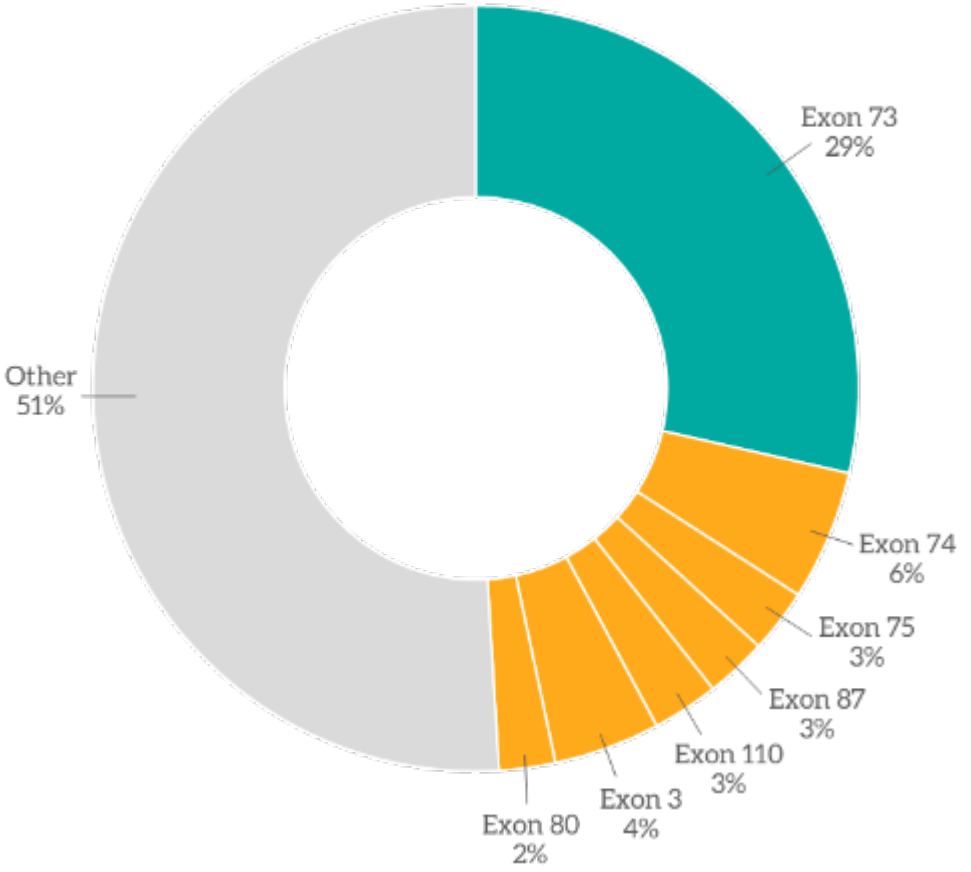
- QR-313 is effective in exon exclusion in wild type human fibroblasts in vitro
- QR-313 is effective in exon exclusion in full thickness skin models in vitro
  - Diffusion of QR-313 in “blister like” dermis
  - Exon skipping demonstrated
- Collagen type VII missing exon 73 can form anchoring fibrils (literature)
- QR-313 is delivered to (epi)dermis in vivo
- Formulation in hydrogel is feasible and stable
- Off-target immunogenicity was not observed

3. Clinical development strategy

- Add-on to standard of care
- Topical with low additional treatment burden
- Rapid symptomatic improvement
- Disease modifying potential

Beachhead and Expansion disease strategy starting with Exon 73 program





High level objectives of the QR-313 Program

- Enter the clinic as quickly as possible.
- Test the hypothesis that oligonucleotide-based exon skipping leads to rapid and meaningful clinical benefit to patients.
- The initial clinical trial will focus on accelerating wound healing and reducing morbidity.
- Extended treatment will focus on establishing disease modifying potential through production of stable, functional collagen type VII at the dermal/epidermal junction in areas of skin at risk for blister recurrence.

Progress to the Clinic

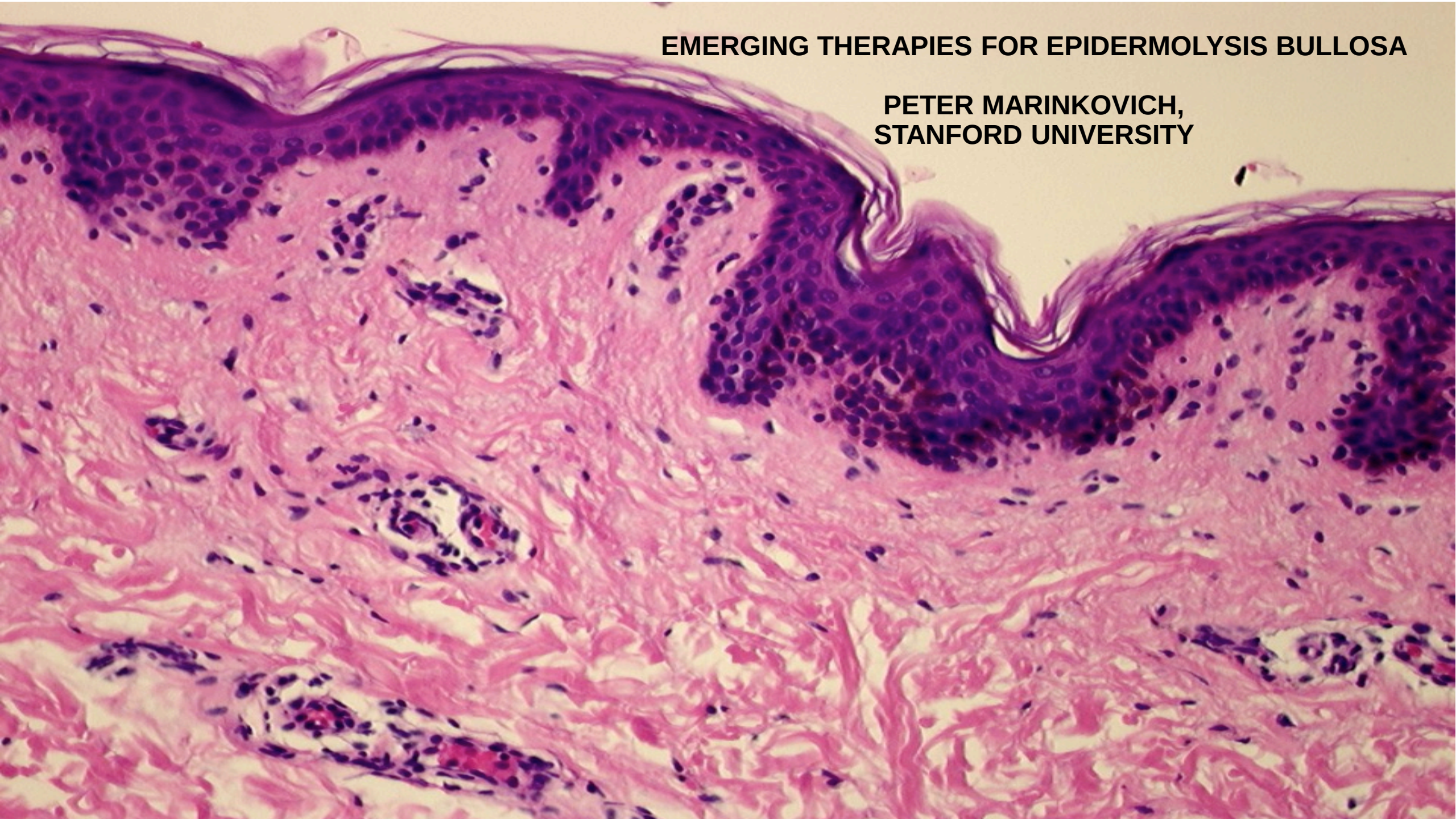
- ✓ Pre-clinical PoC
- ✓ Off-target oligonucleotide class effects screening
- ✓ Delivery mode validated
- ✓ Minipig dermal Single/Multiple dose tolerance study
- ✓ Pre-toxicology regulatory discussions
- ✓ GMP manufacturing
- ❑ Formulation
- ❑ Non-clinical safety studies
- ➢ IND/CTA filing
- ➢ Phase 1/PoC trial start

Thank you!

Patients and families who have been so supportive of our efforts.

Care Givers who have encouraged us to pursue this very rare indication.

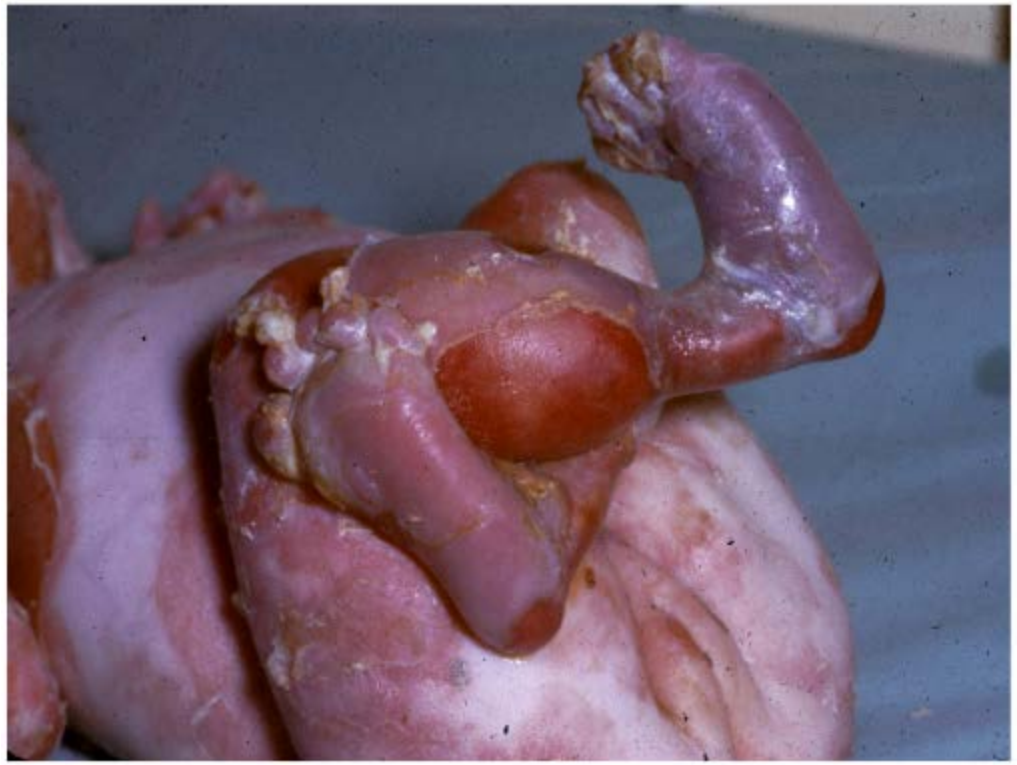
Regulators who are willing to help us address the challenges of ultra-rare disease drug development.



EMERGING THERAPIES FOR EPIDERMOLYSIS BULLOSA

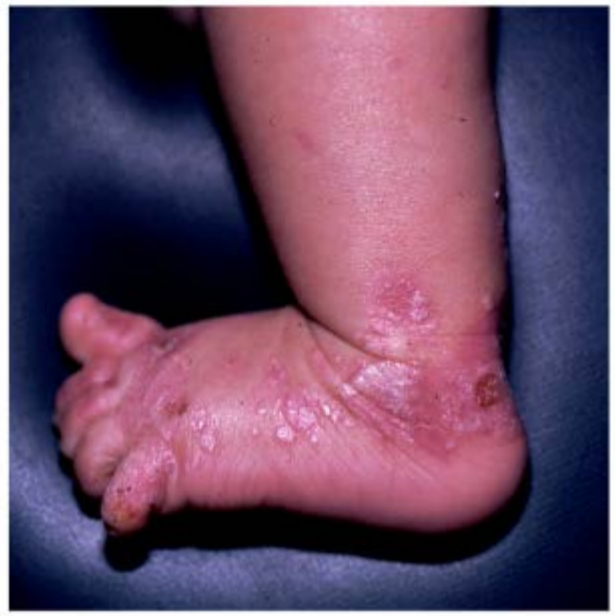
PETER MARINKOVICH,
STANFORD UNIVERSITY

Spectrum of recessive dystrophic EB (RDEB)

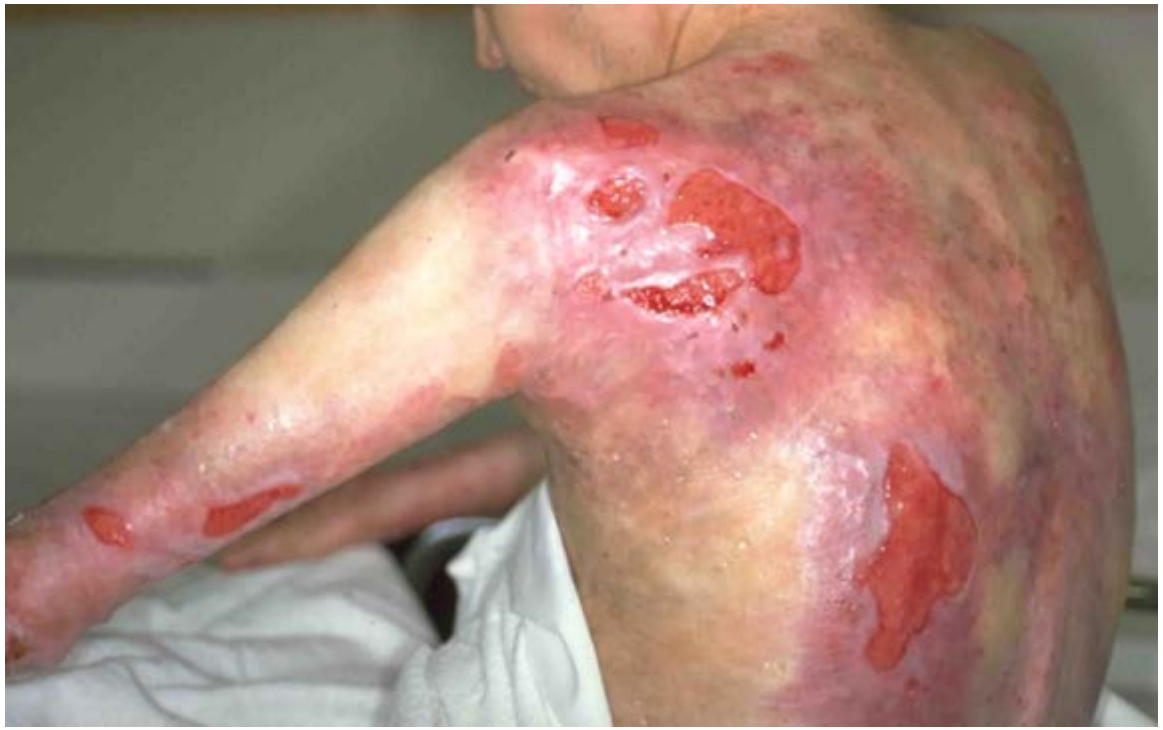


Severe RDEB with congenital loss of skin

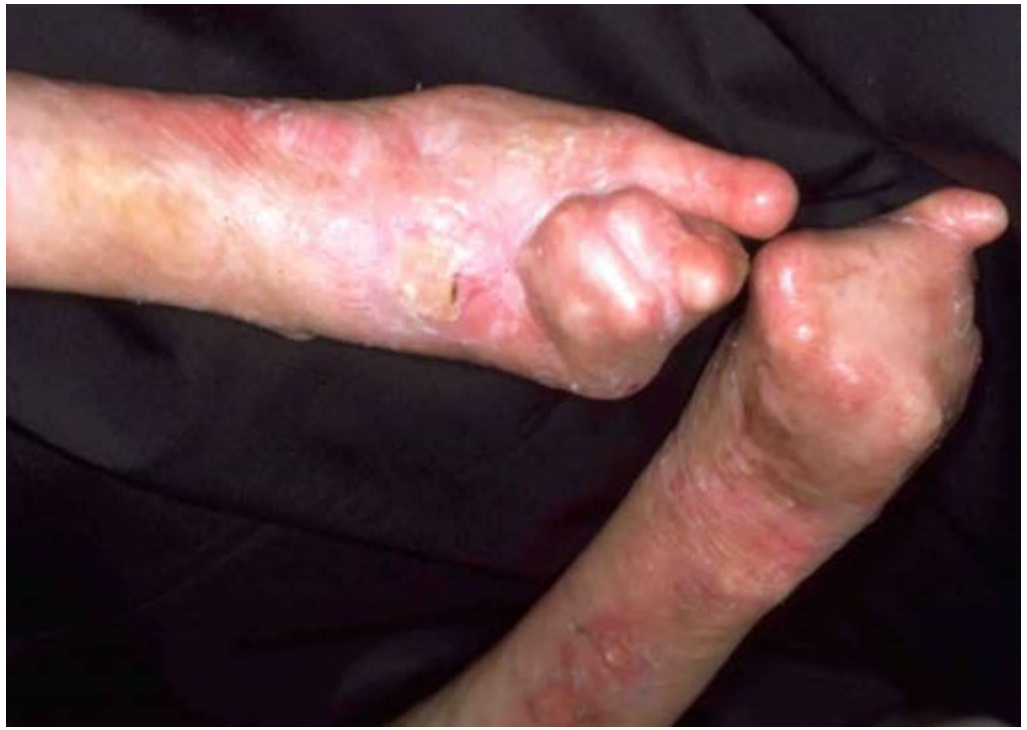
Mild RDEB with mila



Severe generalized recessive dystrophic epidermolysis bullosa

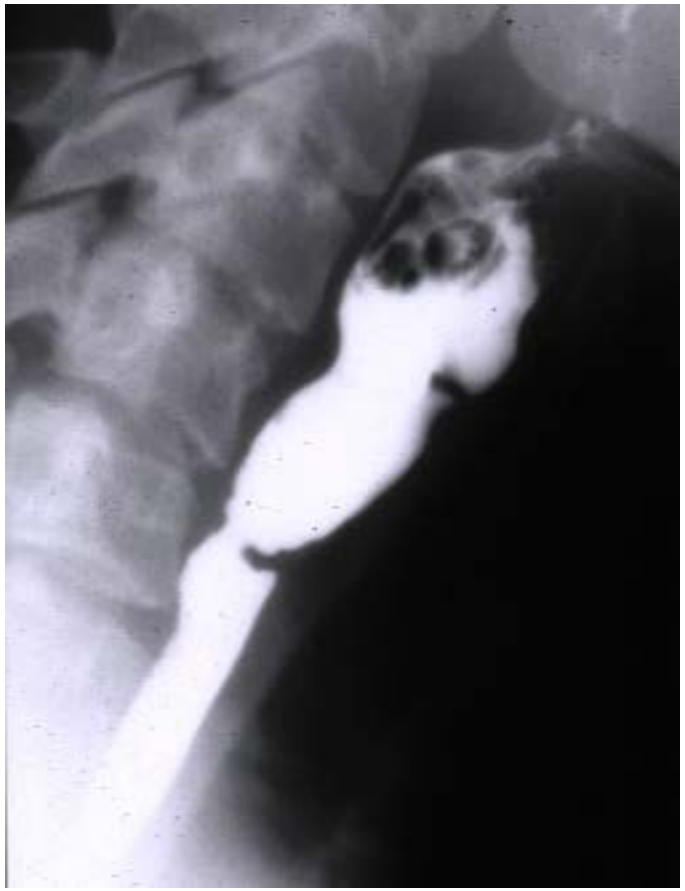


Widespread erosions and scarring

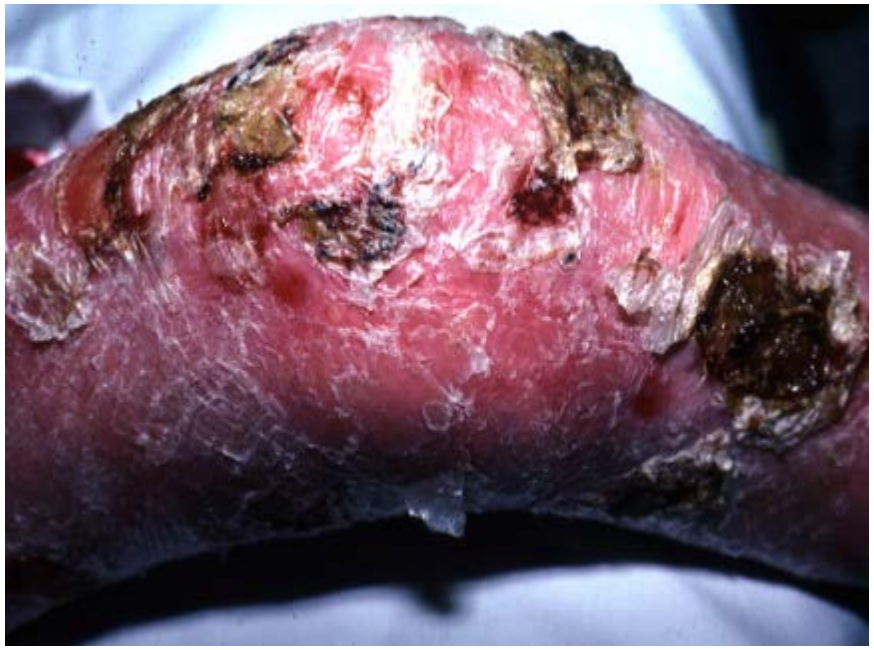


Mitten hand scarring of hands

Complications of RDEB

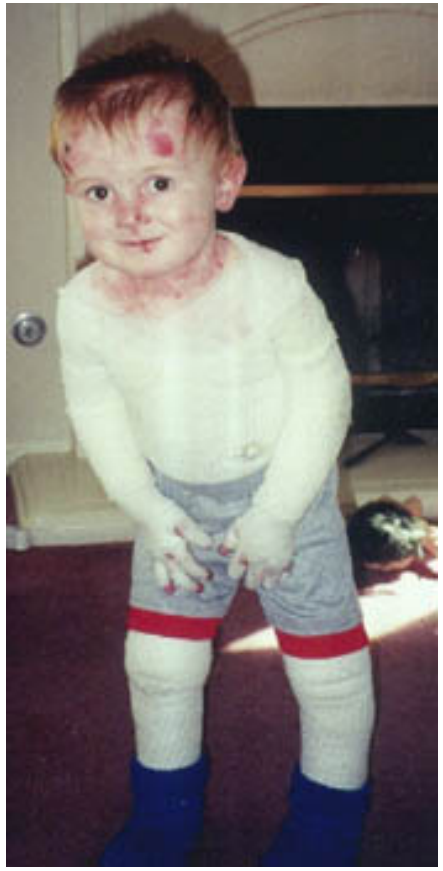


Tracheal or esophageal strictures



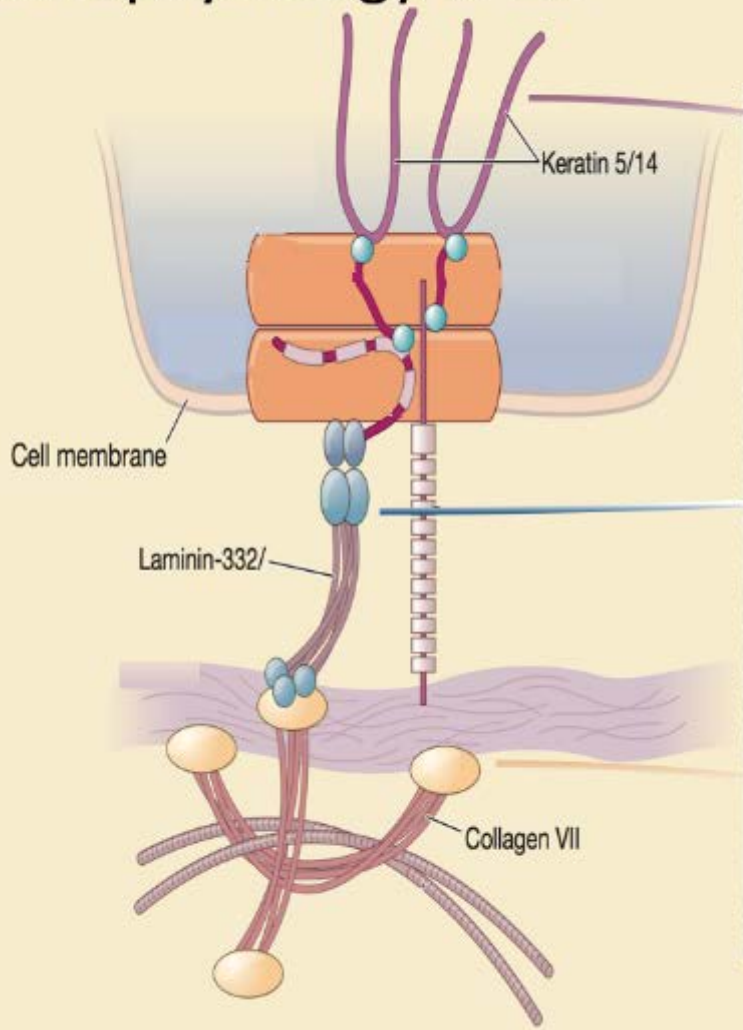
Squamous cell carcinoma

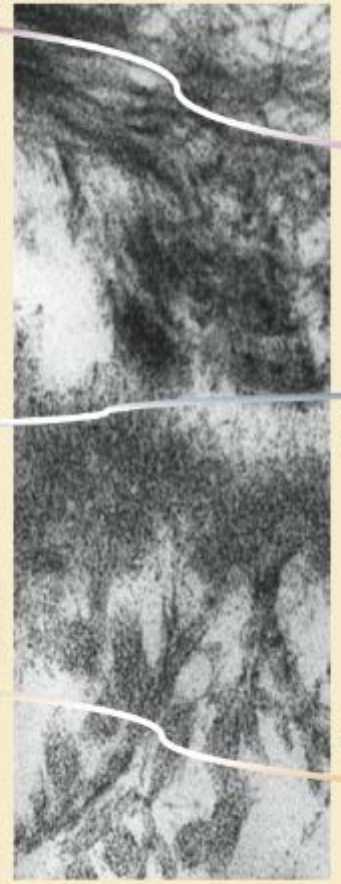
Treatment of EB



- Wound care -nonstick dressings-generous ointments-no tape!
- Infection- look for and treat!
- Nutrition-optimize!
- Anemia
- Squamous cell Ca

Pathophysiology of EB

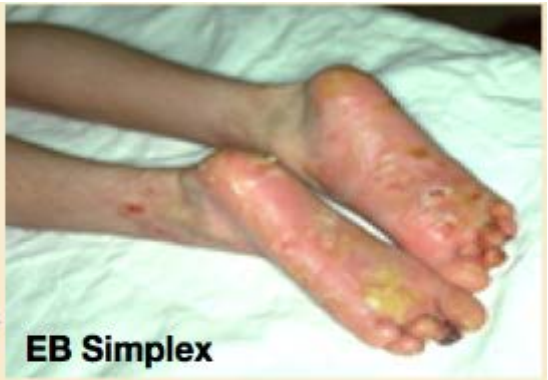


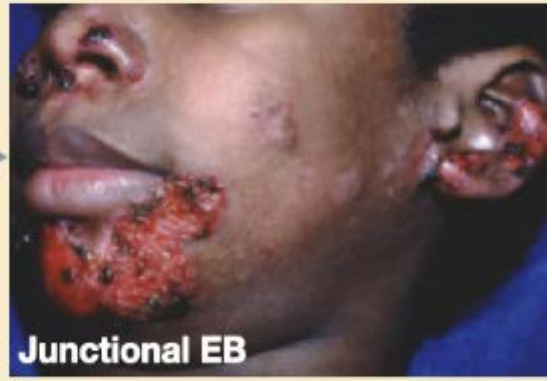


Intermediate filaments

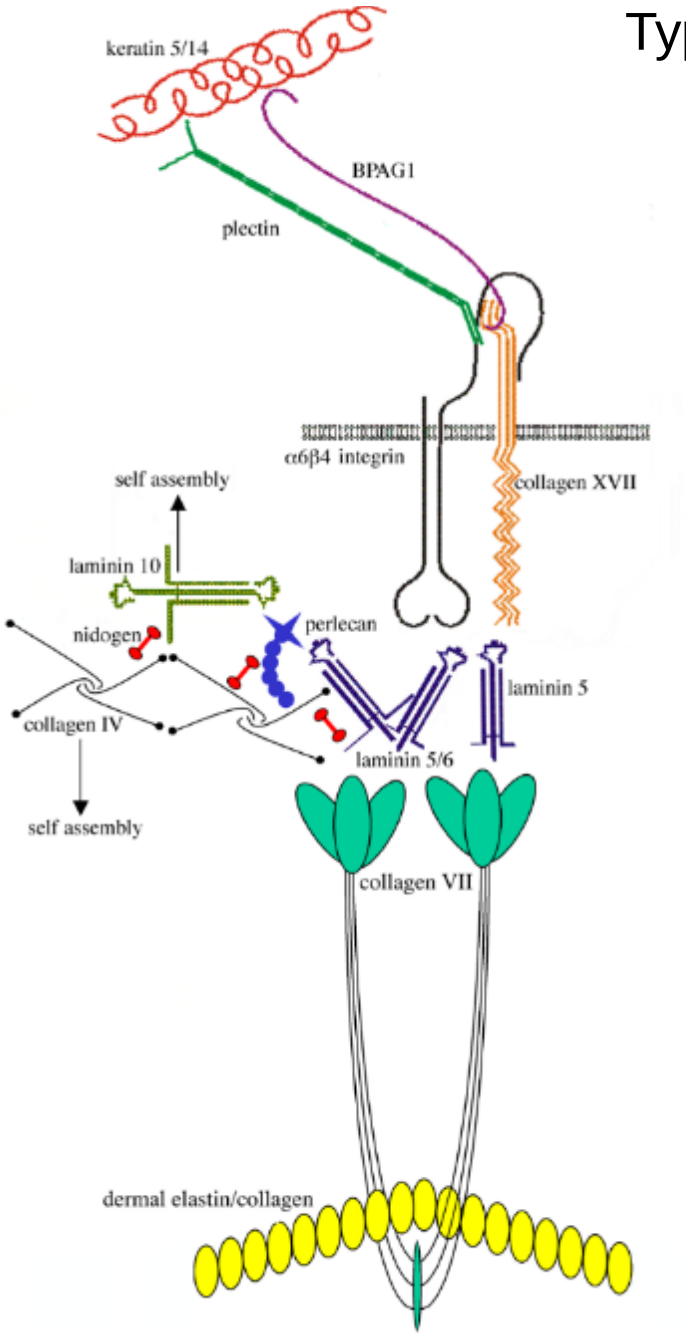
Anchoring filaments

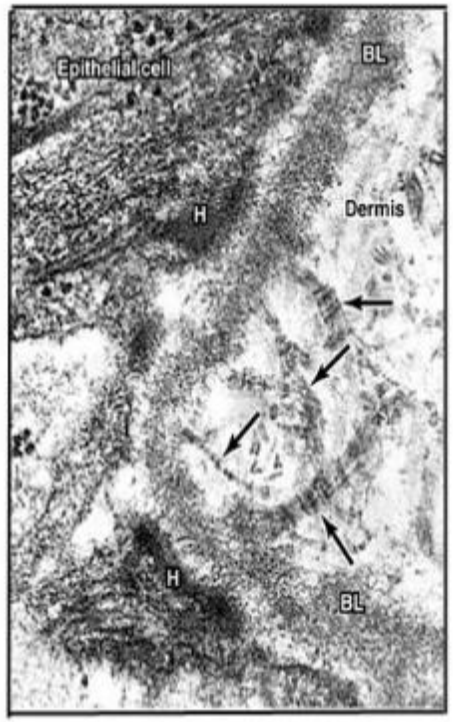
Anchoring fibrils





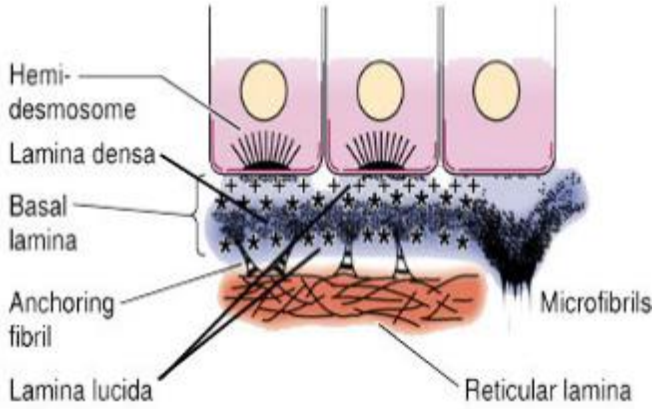
Type VII collagen and anchoring fibrils

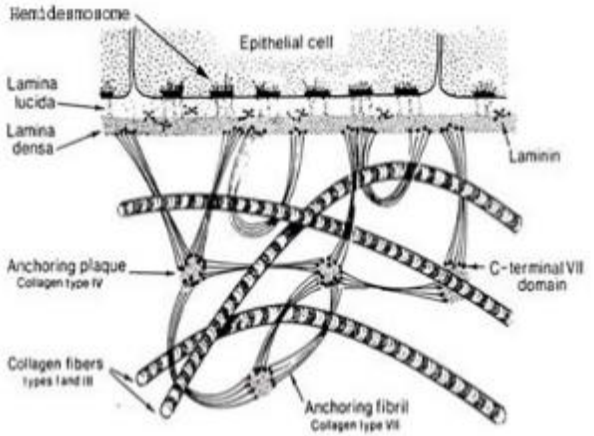




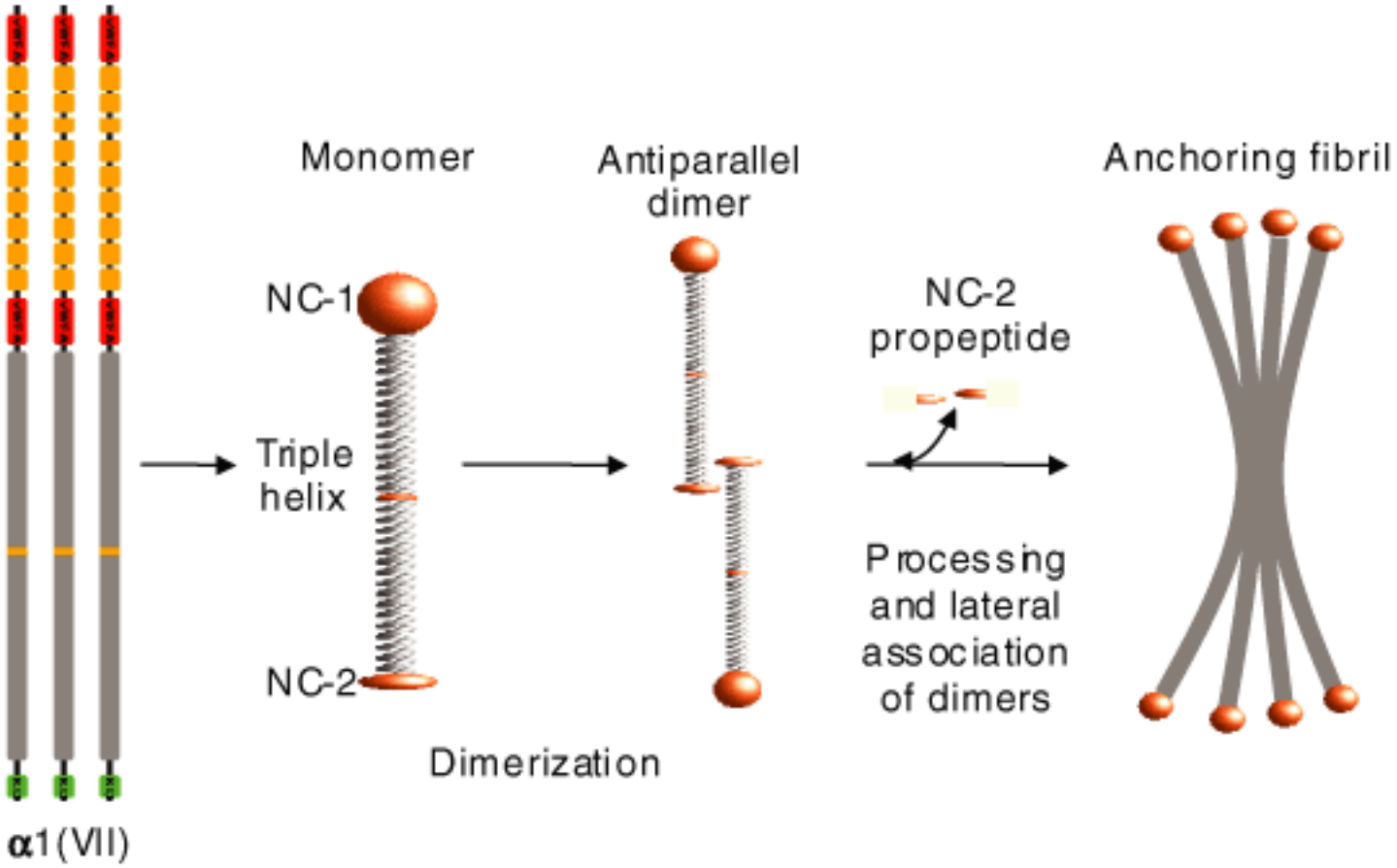
BL = Basal lamina
H = Hemidesmosome
= anchoring fibrils

The Ultrastructure of Basal Laminae
(from Basic Histology, 10th edition)

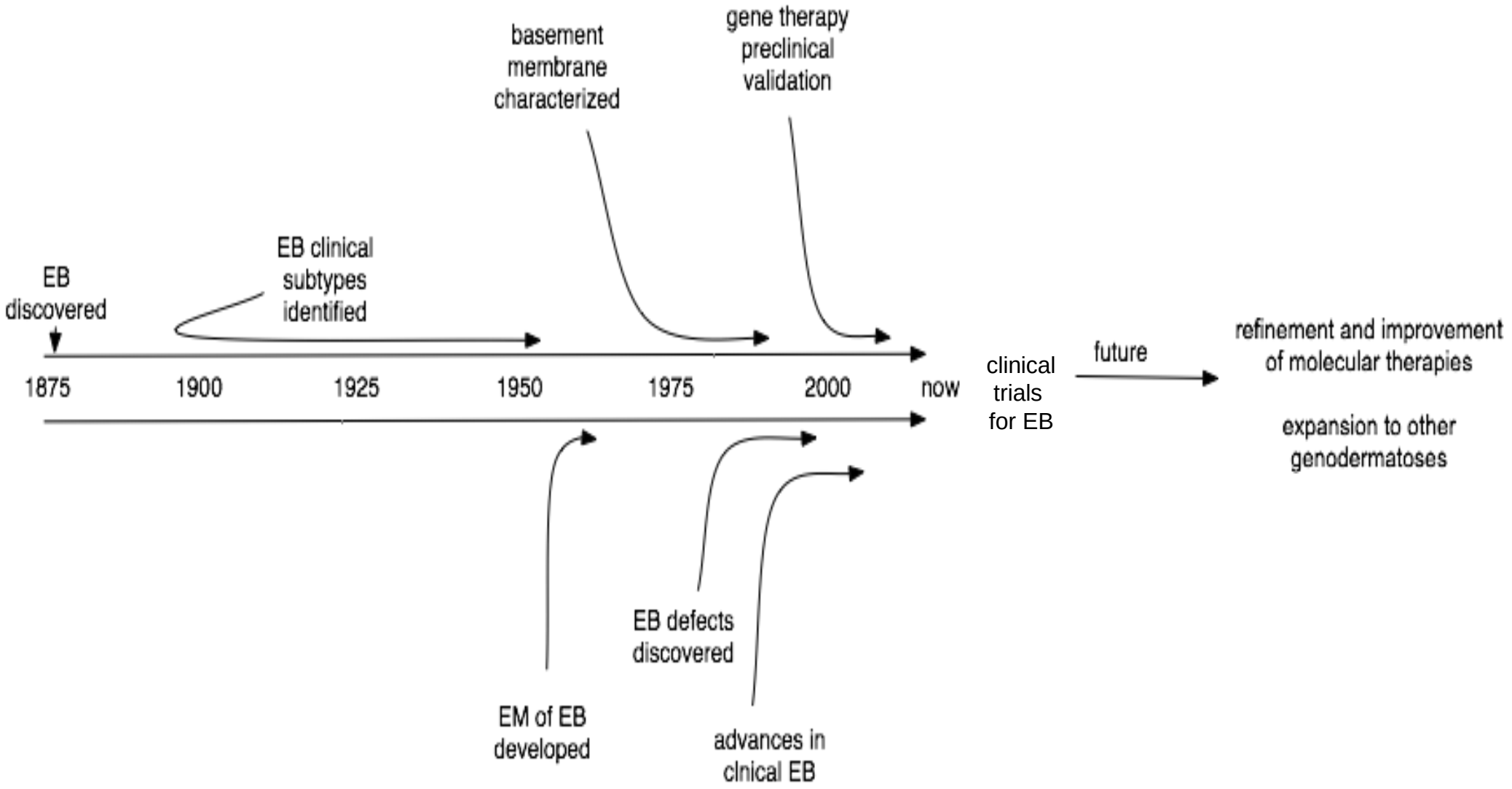




type VII collagen: anchoring fibril assembly



Road to molecular therapy for epidermolysis bullosa



Overview of emerging therapies for epidermolysis bullosa

In clinical trials

Anti-inflammatory therapies: topical allantoin, topical diacerin

Allogeneic cell therapies: allogeneic fibroblast injections, mesenchymal stem cell infusions, bone marrow transplantation

Autologous gene therapies: collagen VII engineered keratinocyte sheet grafts, and collagen VII engineered fibroblast cell injections

Emerging/preclnical

Collagen VII protein therapy, induced pleuripotent stem cell therapy, losartan antifibrotic therapy, extension of spontaneously reverted EB skin

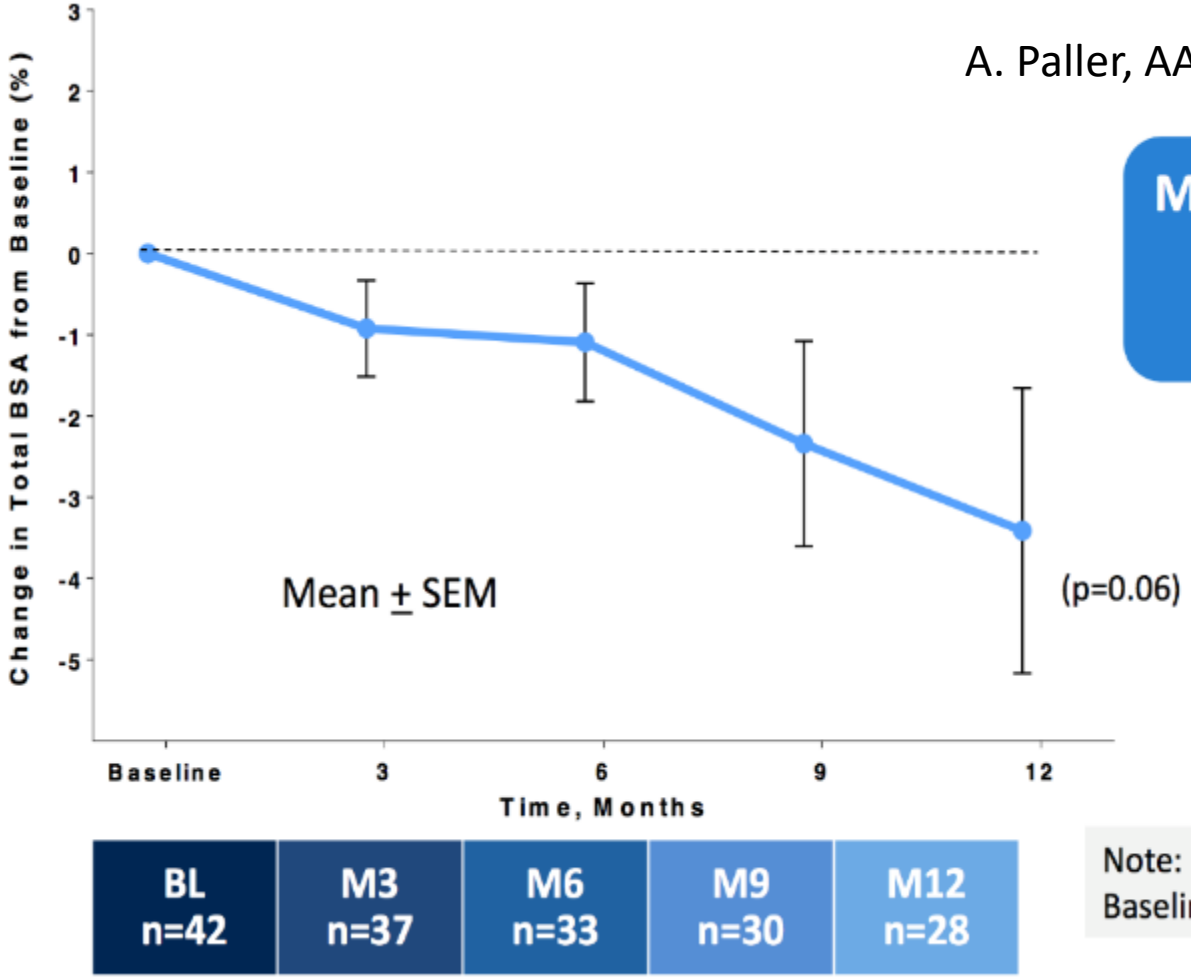
Anti-inflammatory: Topical Allantoin (Zorblisa) Amicus therapeutics

- Completed phase 2b multi-center, double-blind trial in 48 patien with multiple EB subtypes

- End points: target wound healing at 1 month, time to wound closure, change in tota body surface area lesional skin, change i itching, and the safety

- Phase 3 (ESSENCE) trial currently in progress study of EBS, JEB, DEB

A. Paller, AAD presentation March 2016



Mean Absolute Change to Month 12 (95% CI): -3.41% (-7.0, 0.2)

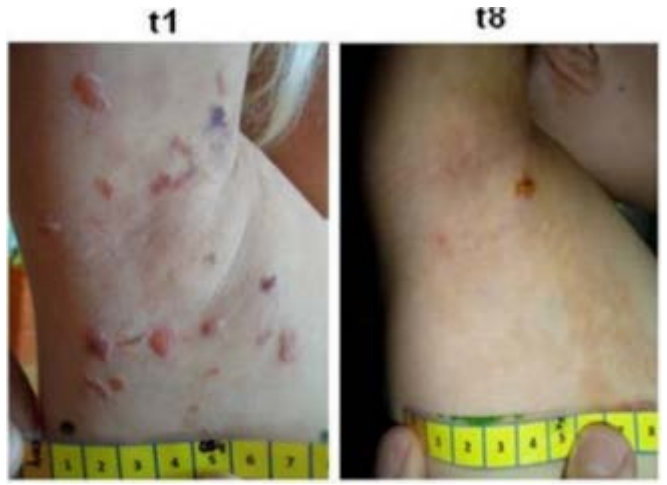
Note: Baseline BSA for entire group = 11.3; Baseline BSA for group at 12 mos. = 10.9

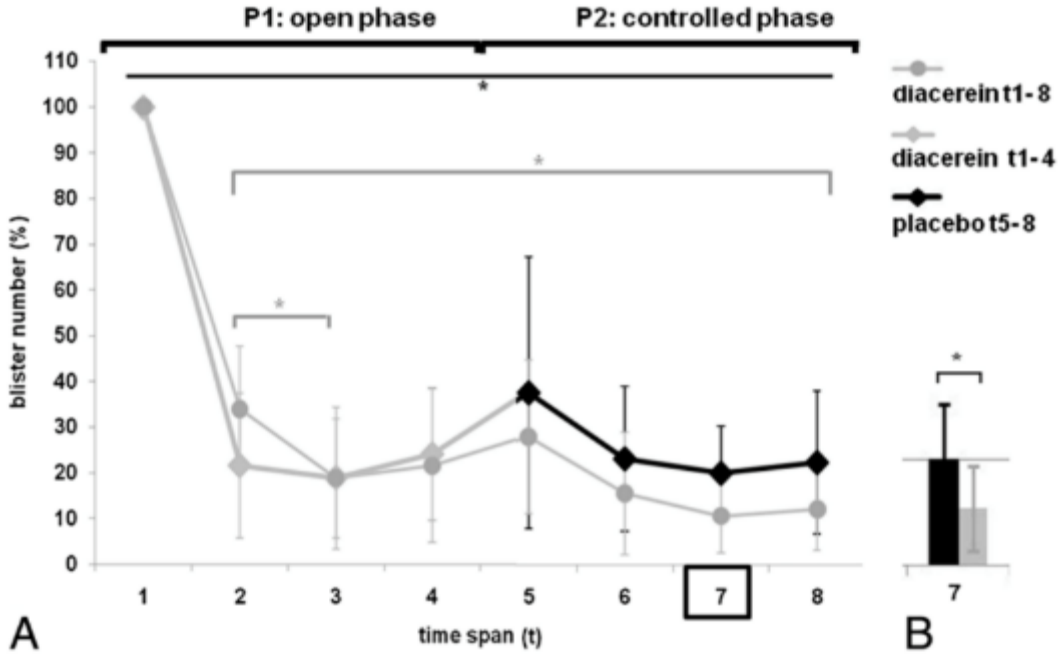
Summary: improvement is modest and does not address disease defect

Diacerin: 1% cream for epidermolysis bullosa simplex

- **Diacerin: an approved systemic treatment for osteoarthritis**
- **5 EBS patients treated in axillary regions diacern vs control vehicle**
- **Reduced blister count over two month time point**
- **Anti-IL-1 effect reduces inflammation in EBS**
- **May have some activity on keratin expression**

Wally et al Orphanet J Rare Diseases 2013

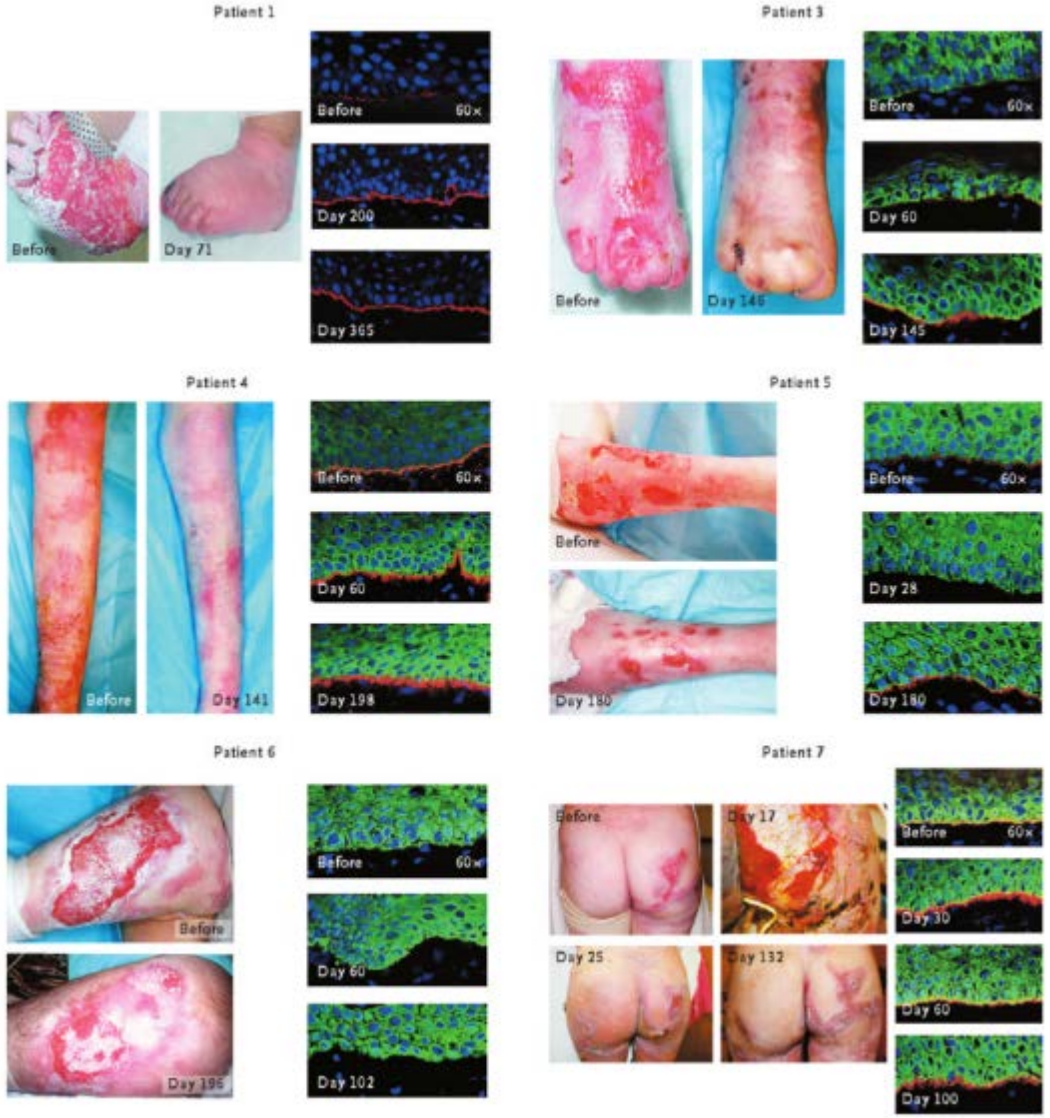




Summary: improvement is modest and does not address disease defect

Bone Marrow Transplantation in recessive dystrophic epidermolysis bullosa

- Seven RDEB patients treated showed varying levels of clinical improvement
- Increased collagen VII expression by bone marrow derived mesechymal cells
- Electron microscopy showed modest changes in anchoring fibrils
- Disadvantages: long term data still pending
- Disadvantages: 30% mortality is greater than mortality of RDEB at ages used



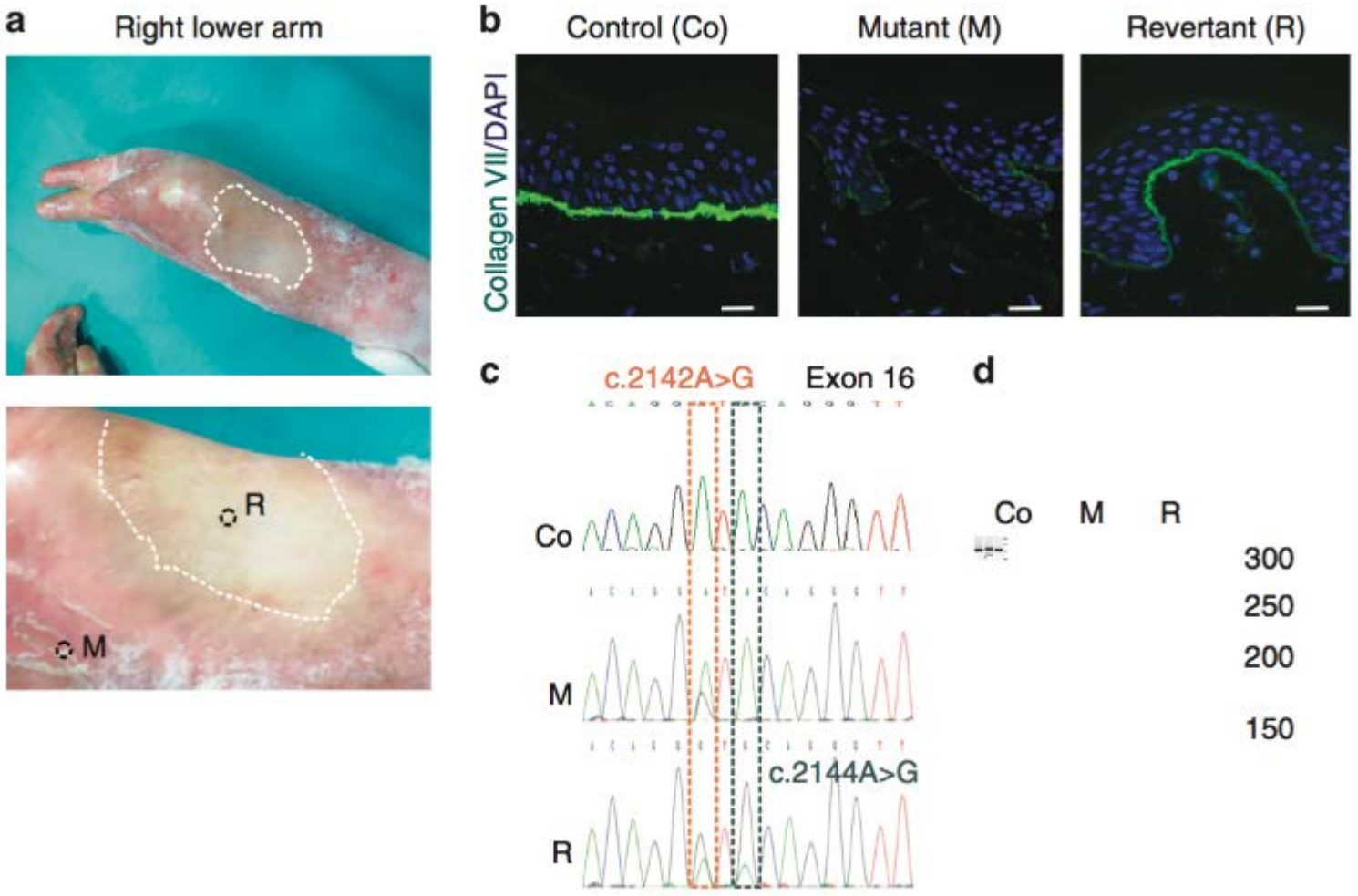
Wagner et al NEJM 2010

Summary: 30% mortality, long term results not known

Revertant mosaicism in epidermolysis bullosa – potential to extend naturally occuring gene corrections

- Observations of focal areas of spontaneous mutation reversion in junctional and dystrophic EB patients
- Common in BP180 deficient JEB (30%), rare in RDEB patients
- Potential to graft corrected areas of skin to non-corrected areas, extending the clinical benefit

Kiritsi et al JID 2014

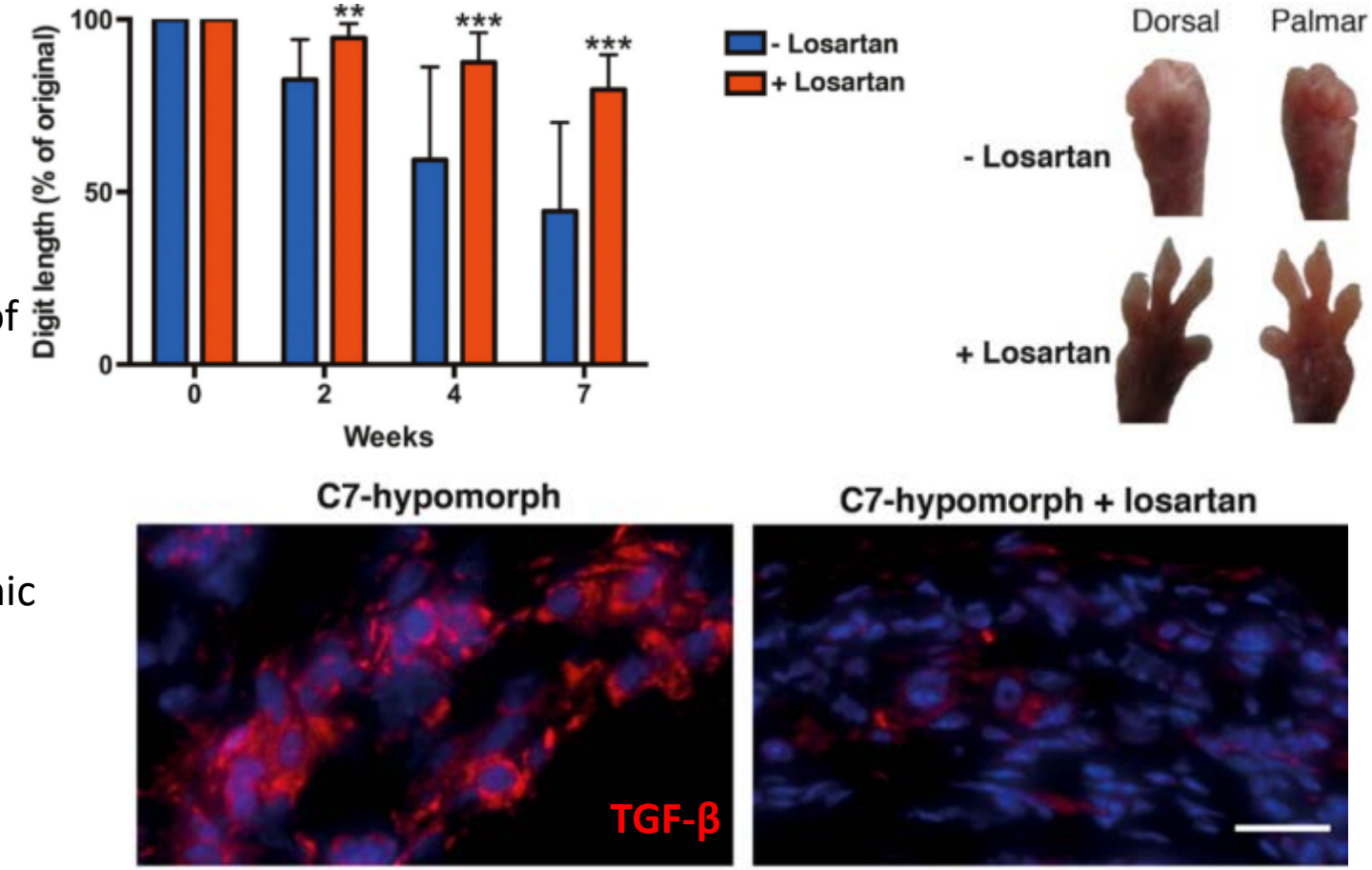


Summary: no reduction to practice yet, very small subset EB patients

Losartan: a potential new anti-fibrotic therapy for dystrophic epidermolysis bullosa

- angiotensin II type I receptor antagonist in clinical use as anti-hypertensive
- inhibited fibrosis and pseudosyndactyly in mouse model of dystrophic EB
- Inhibitor of TGF-β expression
- -Clinical trials of losartan in dystrophic EB patients in Europe

Nystrom et al 2015, EMBO Mol Med



Summary: can reverse fibrosis but not the blistering defect

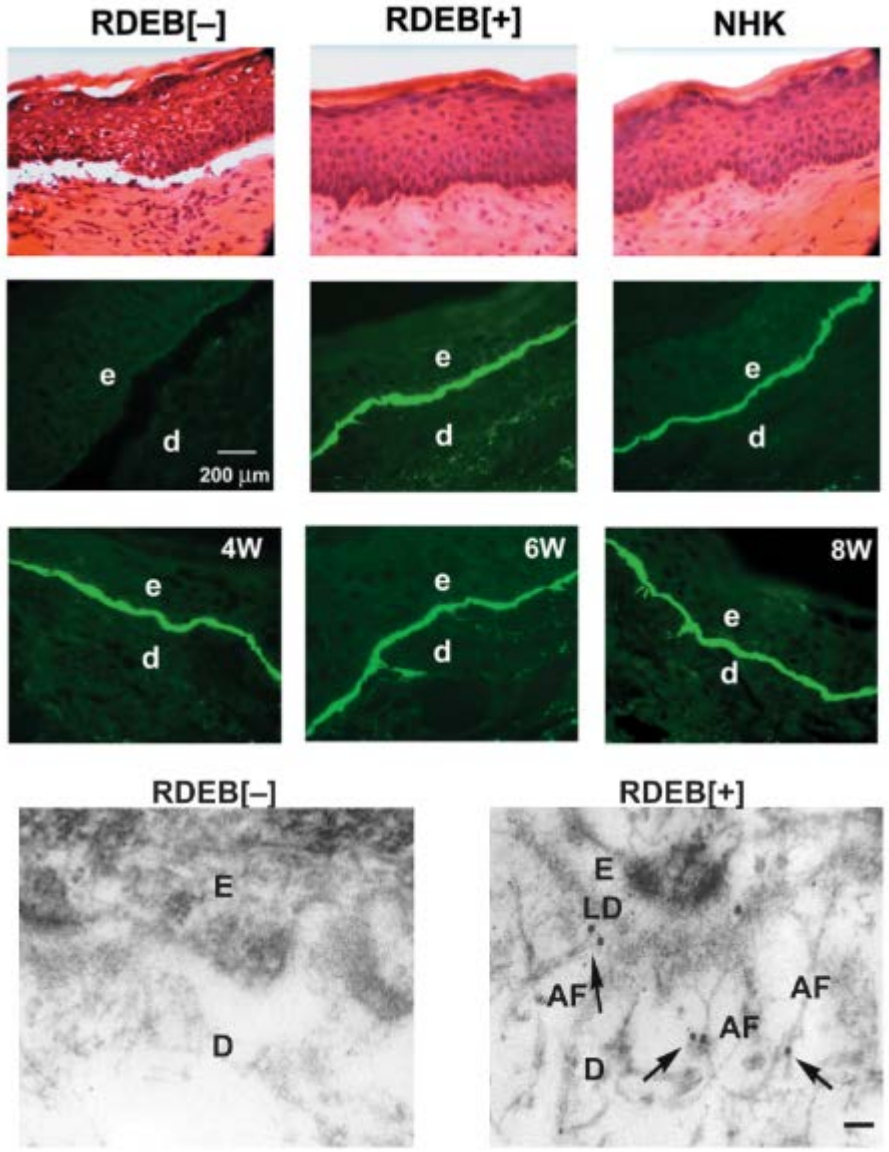
Collagen VII protein therapy for recessive dystrophic epidermolysis bullosa

- Preclinical: intradermal (shown to the right), intravenous, topical collagen VII all shown to be effective

- Shire pharmaceuticals in development of intravenous collagen VII therapy for RDEB, however clinical hold has been put in place for safety issues

- Intra-dermal/intralesional likely to be first route of collagen VII administration in clinical trial of RDEB patients within the next year.

Summary: Expensive and safety issues with IV therapy

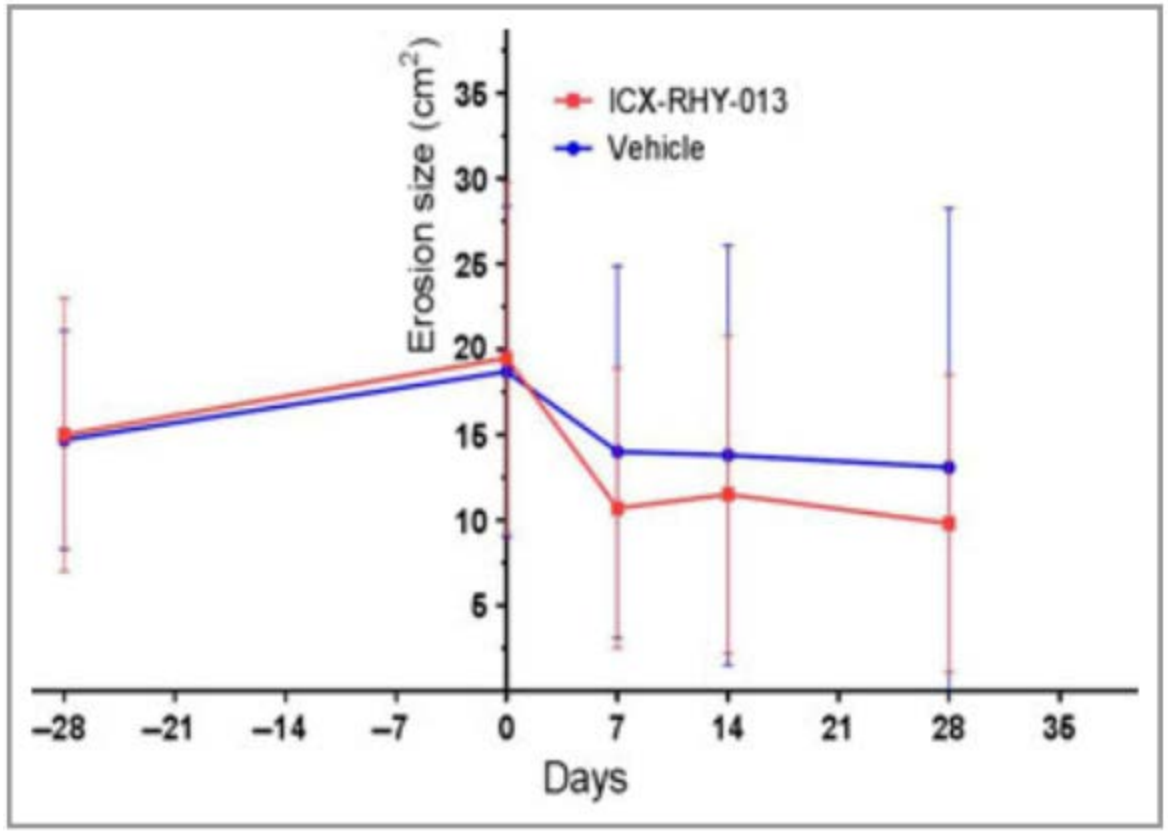


Woodley et al Nat Med 2004

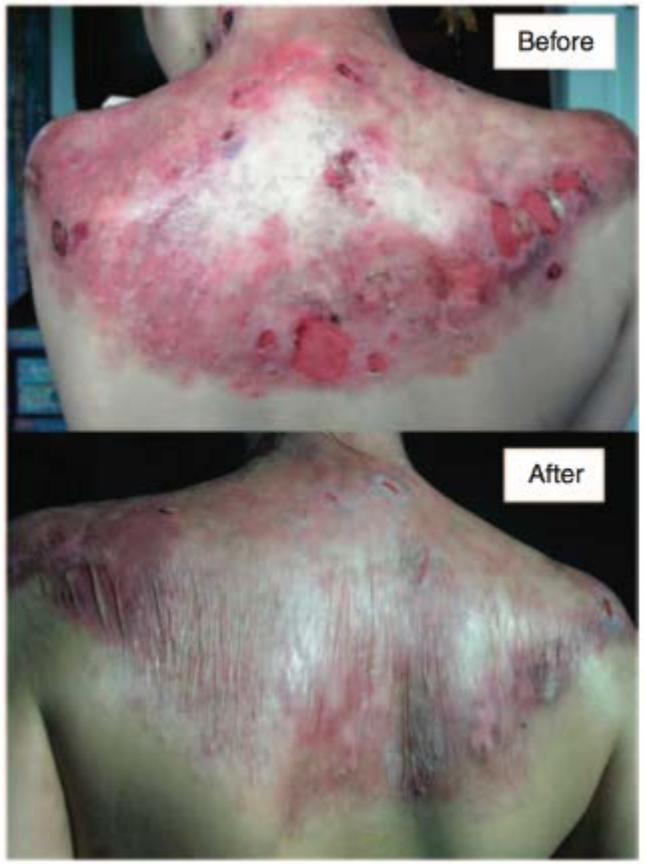
Allogeneic fibroblasts/mesenchymal stem cells for epidermolysis bullosa

Advantages: safe, stimulates short term healing, already in clinical use

Disadvantages: no long term benefit



Intradermal allogenic fibroblast intradermal injections



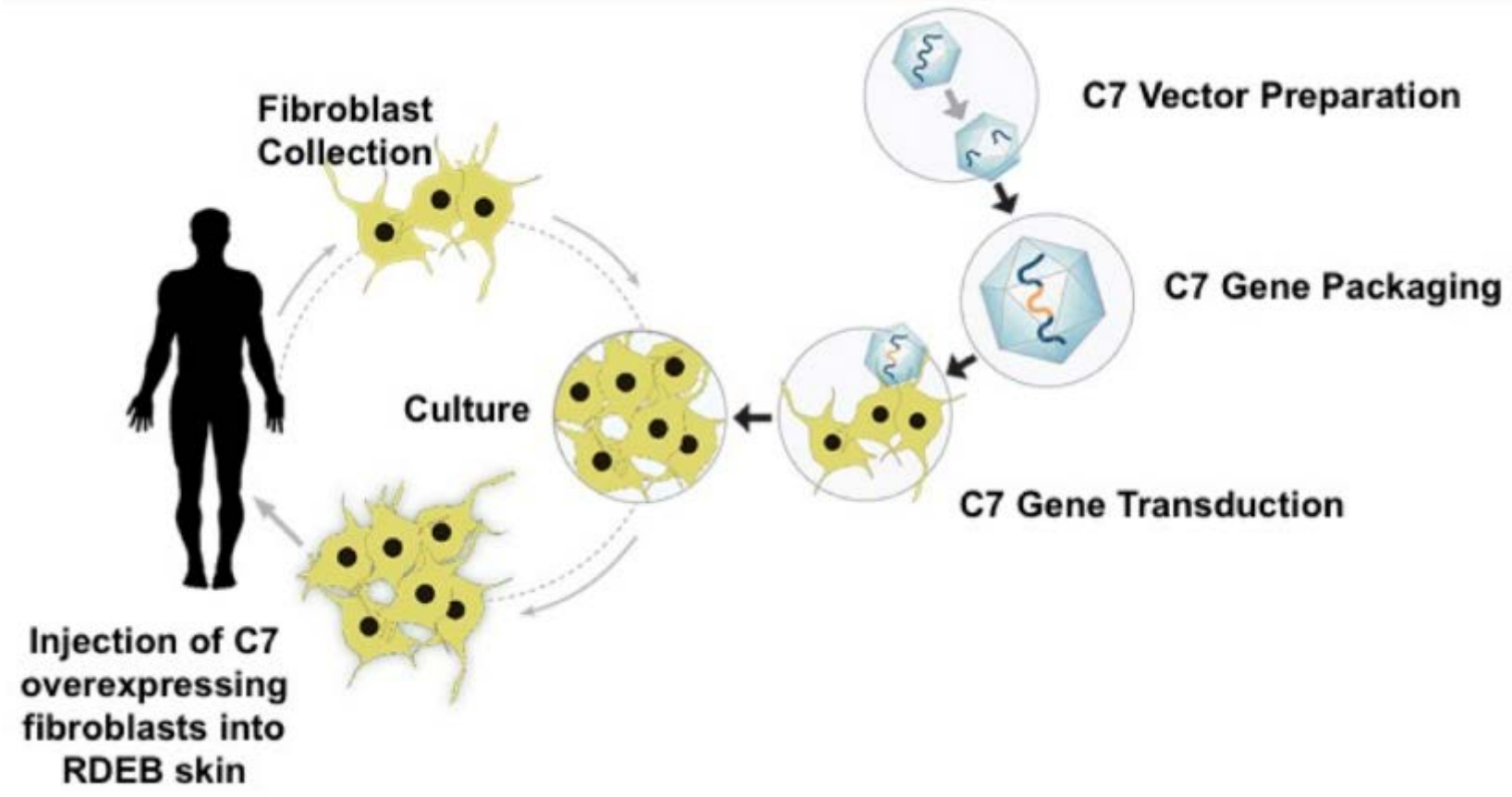
Mesenchymal stem cell IV infusions

Summary: modest results of short duration

Petrof et al 2015 JID; Petrof et al 2013 BJD

Phase I/II trial of C7 Fibroblast Gene therapy for RDEB at Stanford University

- Phase I/II clinical trial of C7 overexpressing autologous fibroblast therapy for RDEB
- Intradermal wound injections of patient derived C7 overexpressing autologous fibroblasts
- Enpoints: Safety, clinical efficacy, molecular correction
- First patient treated last month, 6 patients total planned for 2017 (Fibrocell, sponsor)



JAMA | Preliminary Communication

Safety and Wound Outcomes Following Genetically Corrected Autologous Epidermal Grafts in Patients With Recessive Dystrophic Epidermolysis Bullosa

Zurab Siprashvili, PhD; Ngon T. Nguyen, BS; Emily S. Gorell, MS; Kylie Loutit, BS; Phuong Khuu, MD; Louise K. Furukawa, MD; H. Peter Lorenz, MD; Thomas H. Leung, MD, PhD; Douglas R. Keene, BS; Kerri E. Rieger, MD, PhD; Paul Khavari, MD, PhD; Alfred T. Lane, MD, MA; Jean Y. Tang, MD, PhD; M. Peter Marinkovich, MD

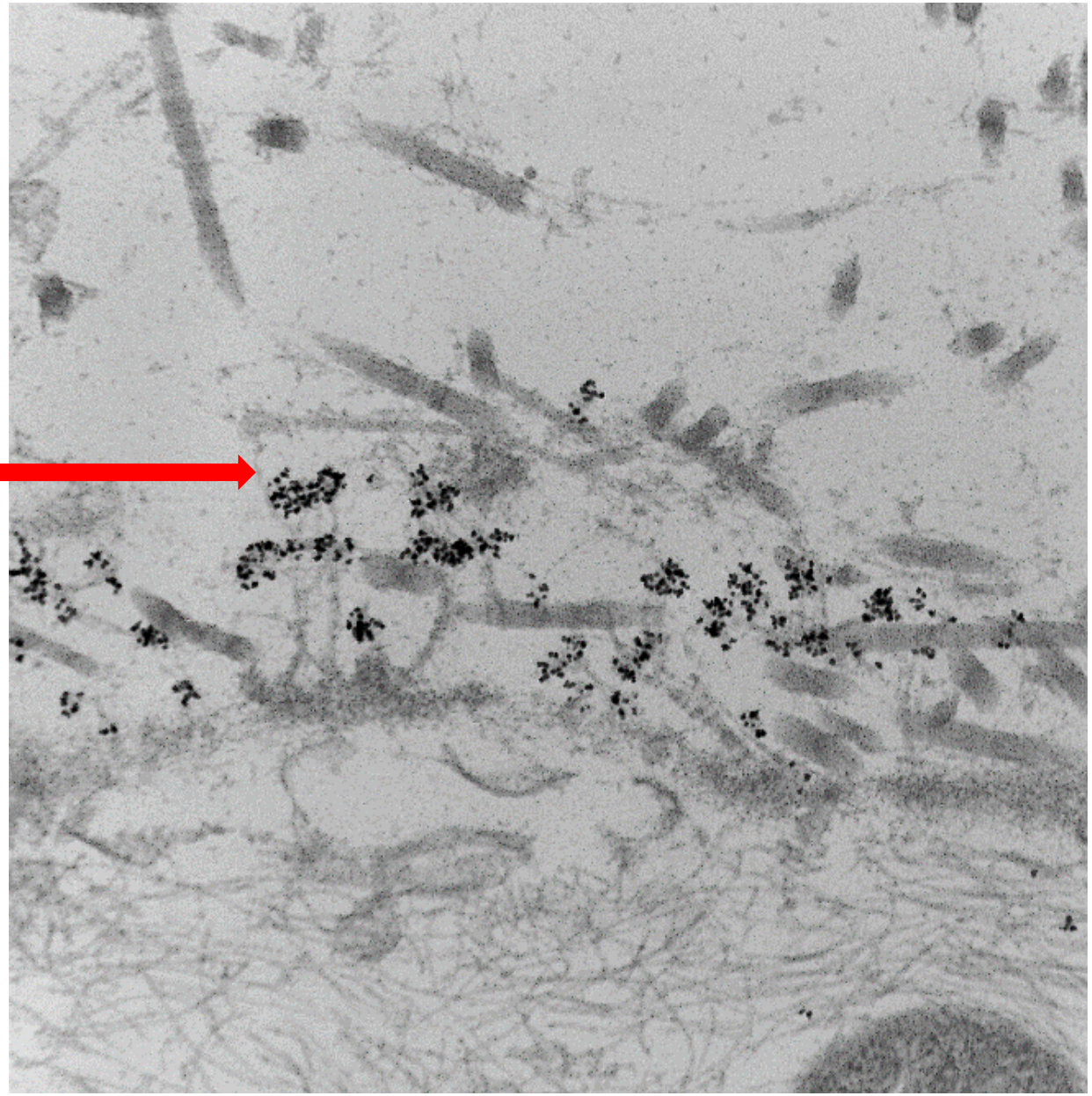
- Results of a phase I trial of epidermal based gene therapy for recessive dystrophic epidermolysis bullosa

- Four RDEB patients treated with C7 engineered autologous keratinocyte grafts six sites per graft, 24 grafts total

- End points: Safety, wound healing efficacy, molecular correction evaluated up to one year

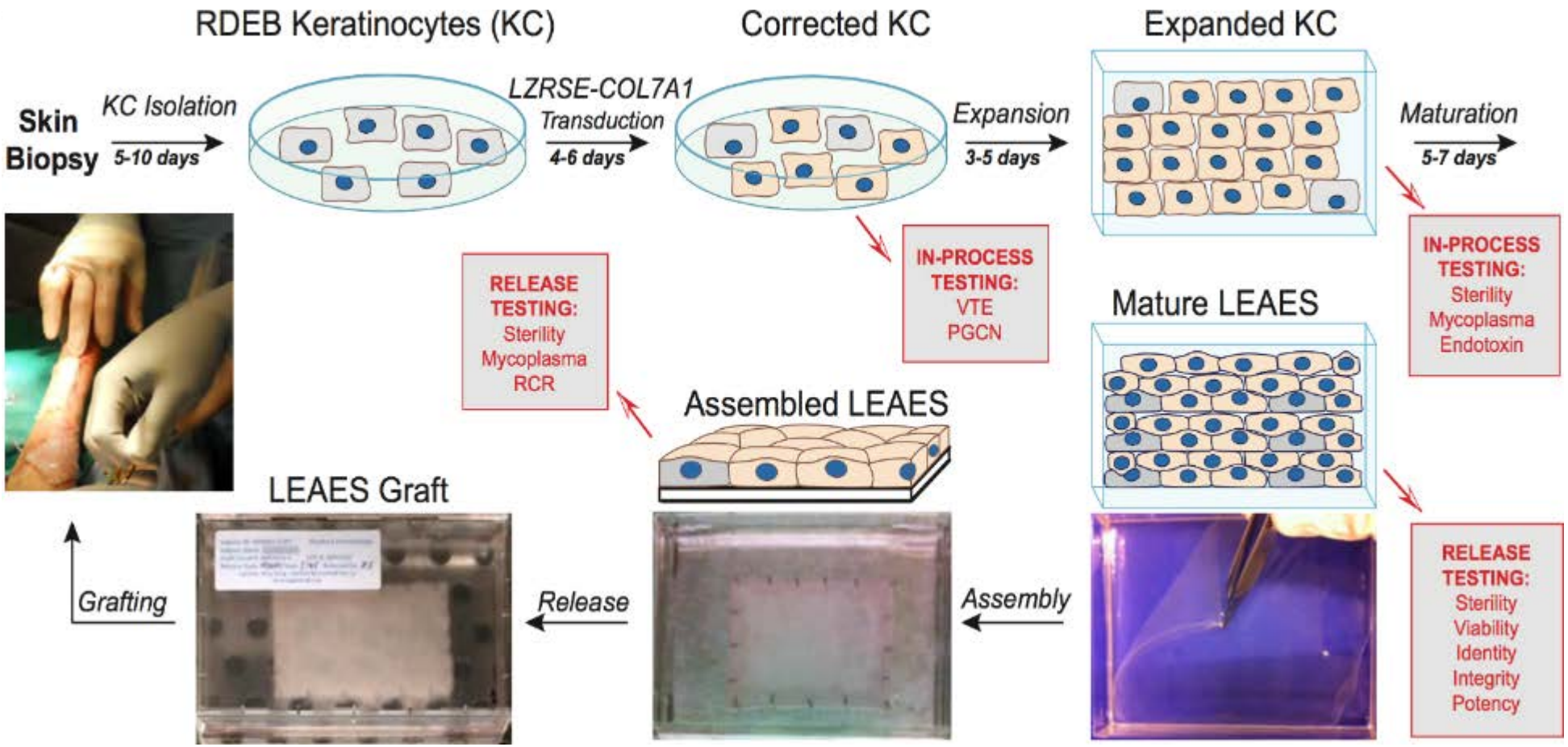
RDEB patient 1
wound correction at
6 months: IEM

LH24
(collagen VII NC2)
immuno-localization



Siprashvili et al, JAMA 2016

Overview of C7 Gene Therapy autograft production



Siprashvili et al, JAMA 2016

Summary: clinically effective but very expensive and highly specialized

Safety analysis of grafted patients

Table 2: Endpoints for Gene Therapy Graft and Systemic Safety

		Systemic Safety Endpoints				Graft Safety Endpoints		
Subject #	Visit	Autoimmune blistering	Circulating auto-antibodies[1]	RCR[2]	Cytotoxic T cells	Graft infection	SCC[3]	Direct auto-antibodies[4]
1	1 mo	-	-	ND[5]	-	-	-	Site E: -
	3 mo	-	-	-	-	-	-	Site D: - Site Z: -
	6 mo	-	-	-	-	-	-	Site E: - Site Z: -
2	1 mo	-	-	ND	-	-	-	Site D: -
	3 mo	-	1:20 IgG	-	-	-	-	Site A: 1+IgG, 1+IgM Site B: - Site E: 2+IgG, trace IgM
	6 mo	-	-	-	-	-	-	Site A: - Site C: - Site D: -
3	1 mo	-	-	ND	-	-	-	ND
	3 mo	-	1:320 IgA	-	-	-	-	Site A: - Site C: -
	6 mo	-	-	-	-	-	-	Site A: trace IgA, trace to 1+ IgM Site B: trace IgM Site D: 1+ IgM
4	1 mo	-	1:160 IgG	ND	-	-	-	-
	3 mo	-	1:160 IgG	-	-	-	-	Site D: 1-2+ IgG, 1+ IgA, trace IgM, 1+ focal C3 Site E: 1-2+ IgG, 1-2+ IgA, 1+ IgM, 1+ focal C3 Site Z: 1+ IgG, 1+ IgA, trace IgM, 1+ focal C3
	6 mo	-	1:40 IgG 1:40 C3	Await	ND	-	-	Await

[1] By indirect immunofluorescence from serum sample on monkey esophagus, autoantibodies localized to basement membrane zone
[2] RCR replication competent retrovirus present in blood
[3] Clinical evidence of squamous cell carcinoma or other neoplasm on graft sites
[4] By direct immunofluorescence performed on skin biopsy, autoantibodies localized to basement membrane zone
[5] ND denotes not done

Siprashvili et al, JAMA 2016

Summary: immune reactions may be an important future challenge

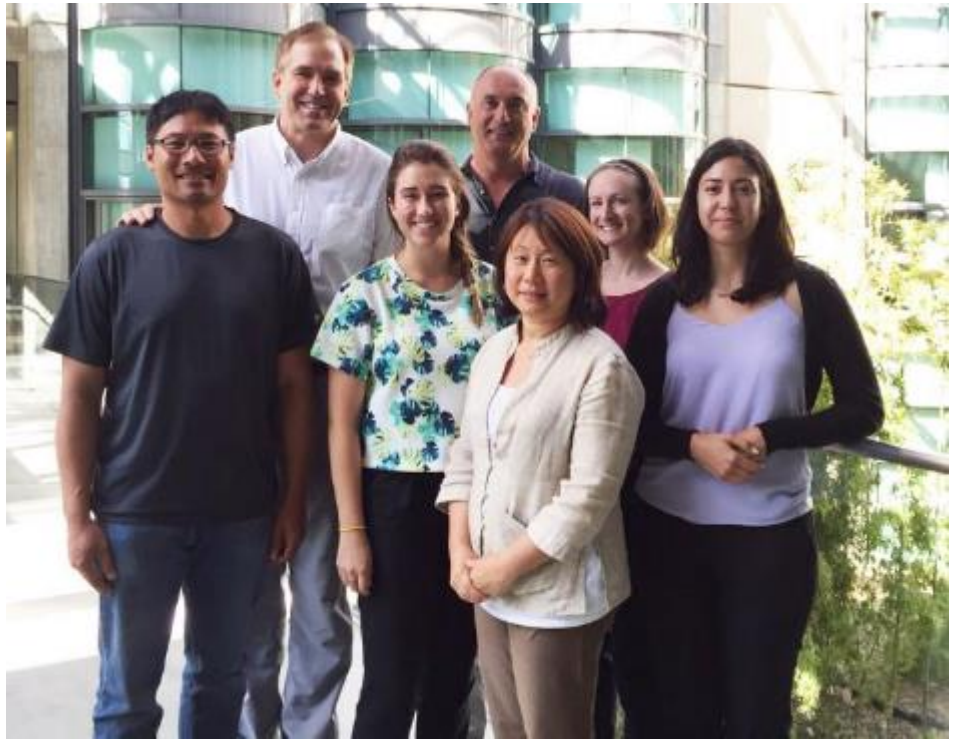
Advantages of ProQR approach

- Corrects underlying defect, unlike diacerin, allantoin or losartan which only address secondary complications
- Topical localized therapy – no need for specialized centers unlike engineered cell therapies
- No insertional oncogenesis, unlike viral based therapies
- Favorable risk/safety profile, unlike bone marrow replacement therapy

Acknowledgements and funding

Stanford EB Team

Jean Tang
Al Lane
Paul Khavari
Doug Keene
Phong Khuu
Zurab Siprashvili
Ngon Nguyen
Emily Gorel
Kylie Loutit
Kerri Rieger
Peter Lorenz
Louise Furakawa
Peter Marinkovich



Lucile Packard Children's Hospital AT STANFORD

EB RESEARCH PARTNERSHIP

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases

debra International

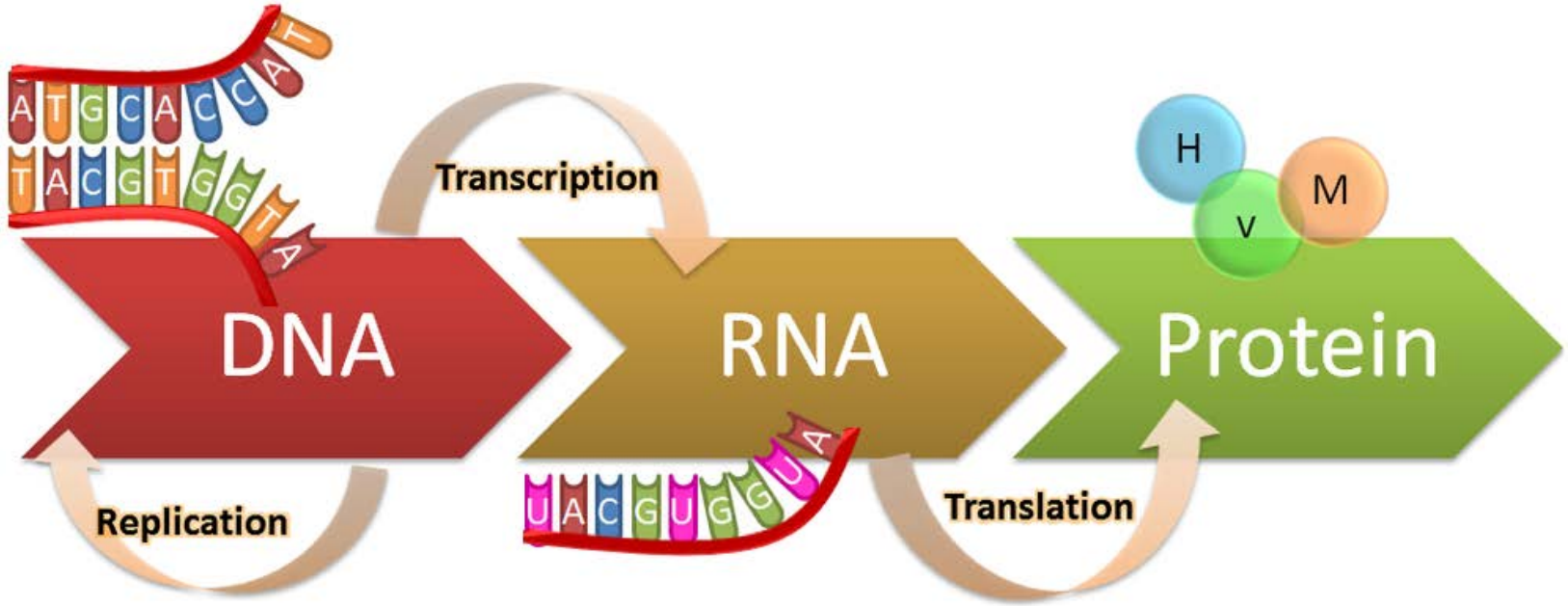
EB & MRF

New Discoveries in Role of RNA Pave Way for Innovative Treatments

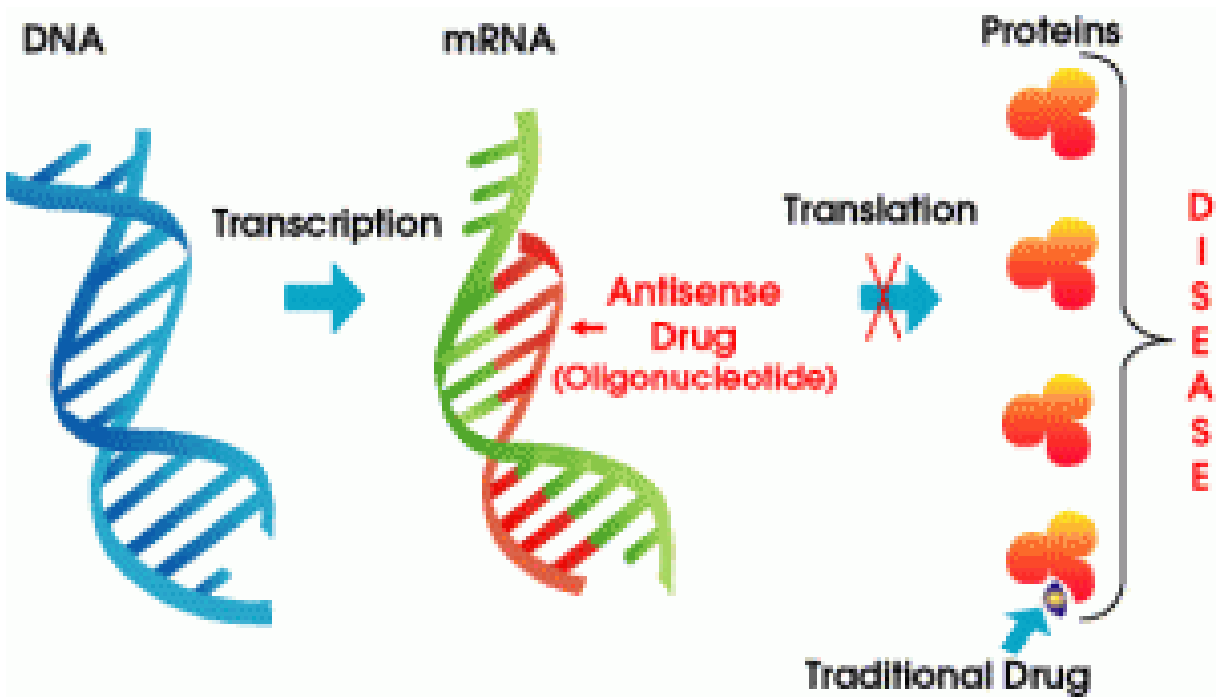
RNA-targeted therapeutics: Past, Present and Future

Arthur A. Levin, Ph.D.
Scientific Advisor & EVP Research and Development, Avidity Biosciences, La Jolla, CA
Art.Levin@gmail.com

Central Dogma of Molecular Biology



RNA-based Drug Discovery & Development



RNA Therapeutics Based on Central Dogma

- Watson and Crick **base-pairing rules have been the foundation** used to develop RNA therapeutics
- Rational drug design – heavily dependent on the central dogma: DNA-RNA-protein
- Use **genomic information to rationally design drugs** that selectively inhibit disease-related RNAs
- In classic pharmacology terms
  - Receptor => Disease related RNA
  - Drug => Oligonucleotide
  - Binding motif => Watson Crick Binding
  - Post binding event => Degradation of mRNA or mods to RNA activity

Evolution of Central Dogma - RNA Role in Nature/Biology More Critical and Complex

- Evolution of Central Dogma: Nature uses RNA as a means of **regulating biology** in multiple ways
- RNA is not just a recipe for proteins it has regulatory functions
- Wealth of regulatory processes and mechanism by which RNAs regulate biology provides **a rich source of novel targets and mechanisms to modulate disease related protein expression**

RNA Role in Regulating Biology Provides New Treatment Opportunities

DNA → RNA →Protein

- One gene to one RNA to one Protein

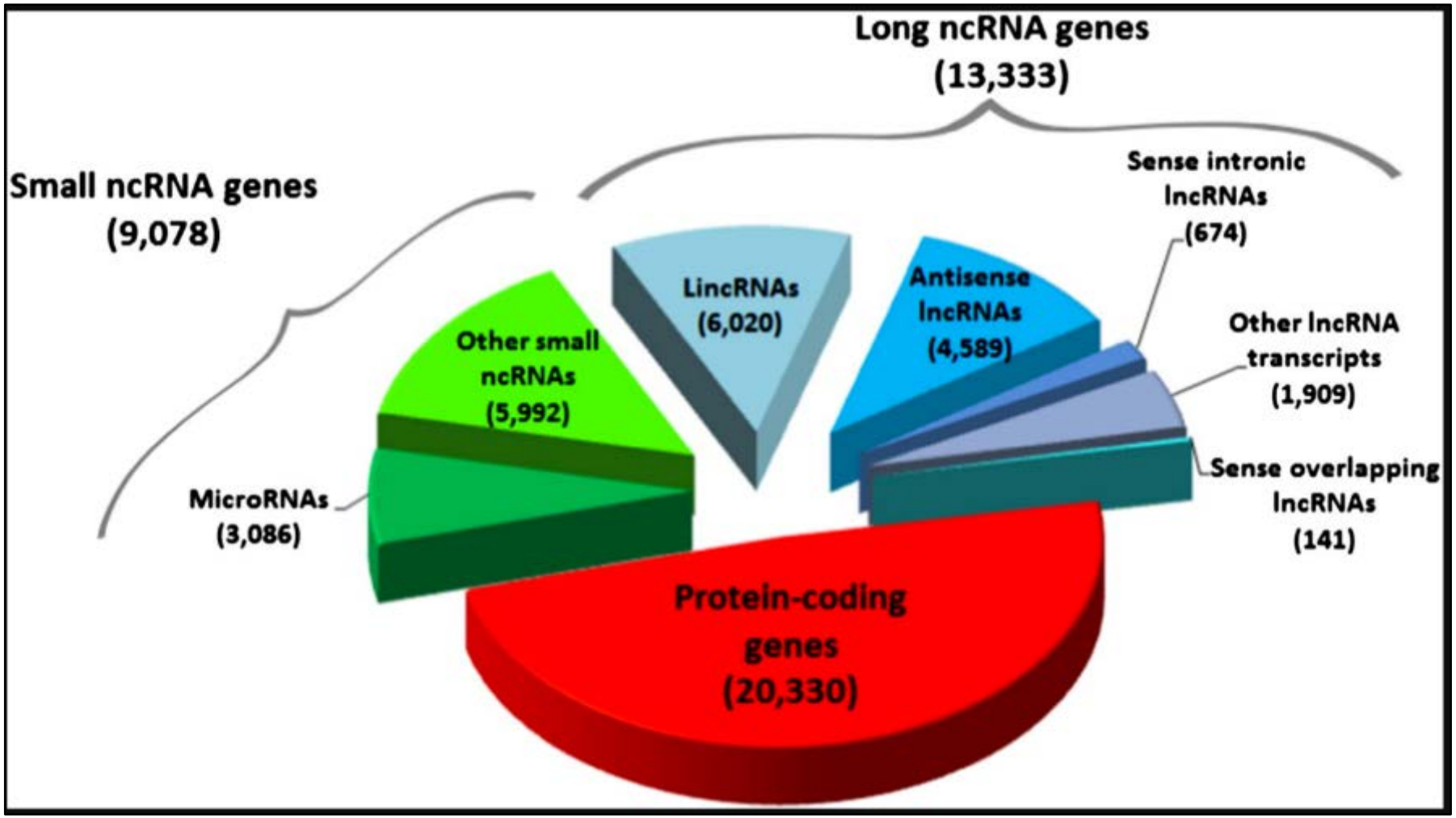
DNA →multiple splice variants → multiple proteins

- One gene, multiple RNAs to multiple proteins with protein expression (transcription factors etc) controlling the entire process

DNA→ mRNA, microRNA, non-coding RNAs→ proteins

- One gene multiple RNAs to multiple protein with proteins, microRNAs, and other RNA-RNA interactions controlling gene expression

Junk DNA No More: Large Portion of the Genome is Non-Coding RNAs



From: Barbara Hrdlickova et al

A New Understanding of RNA Provides Opportunity for Drug Discovery & Development

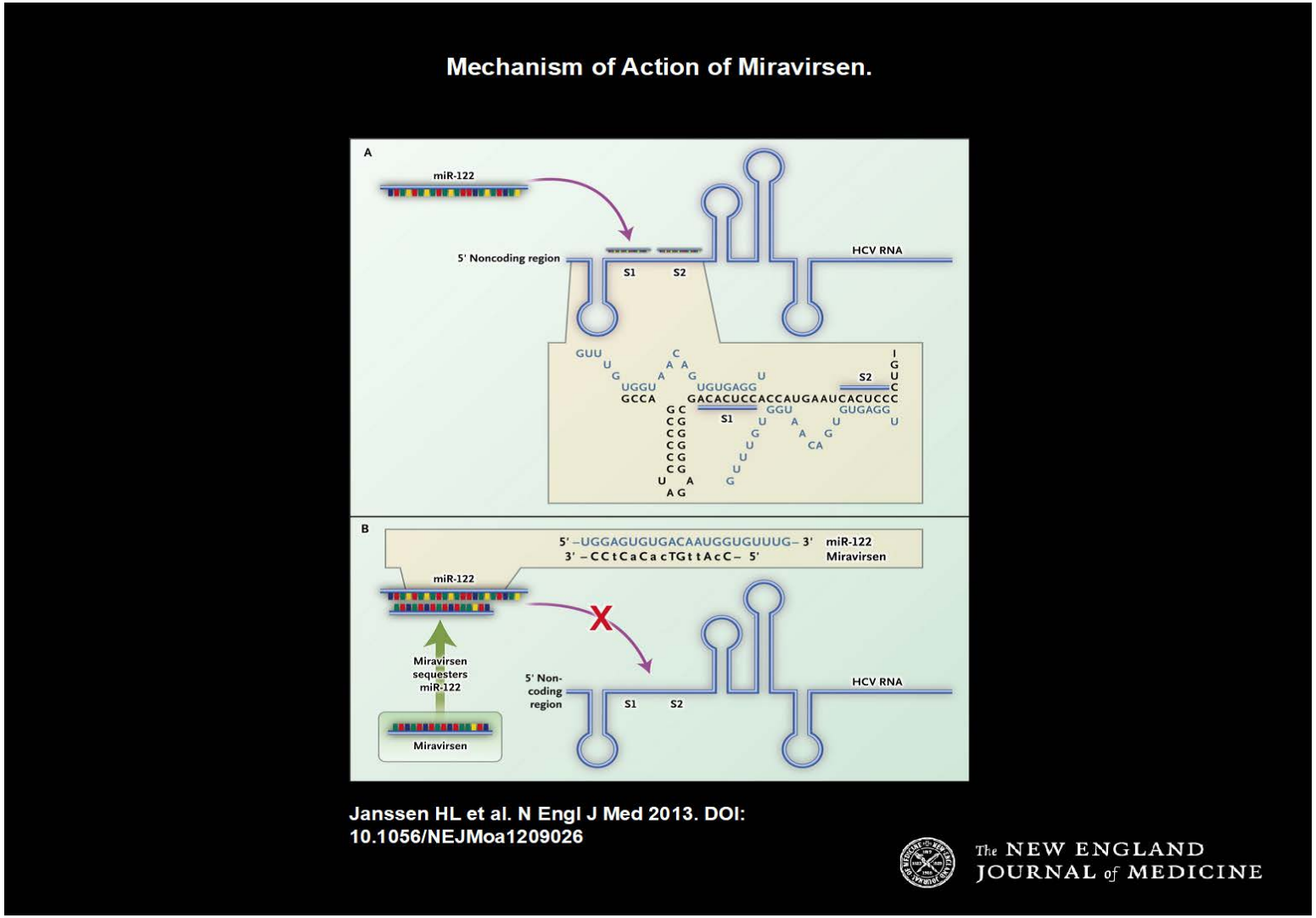
- Watson and Crick base-pairing rules and evolution of **understanding RNA provide ability to create therapeutic agents** to target regulatory RNAs and modulate their function
- **Nature uses RNA as a weapon** in viruses and in viral defense strategies
- Exploit our understanding of these processes to harness some of the regulatory power of RNAs to modulate the expression of disease-related proteins
- Oligonucleotide therapeutics are poised to exploit new knowledge of **RNA's many important roles for therapeutic purposes**

Range of RNA Mechanisms Key in Drug Discovery & Development

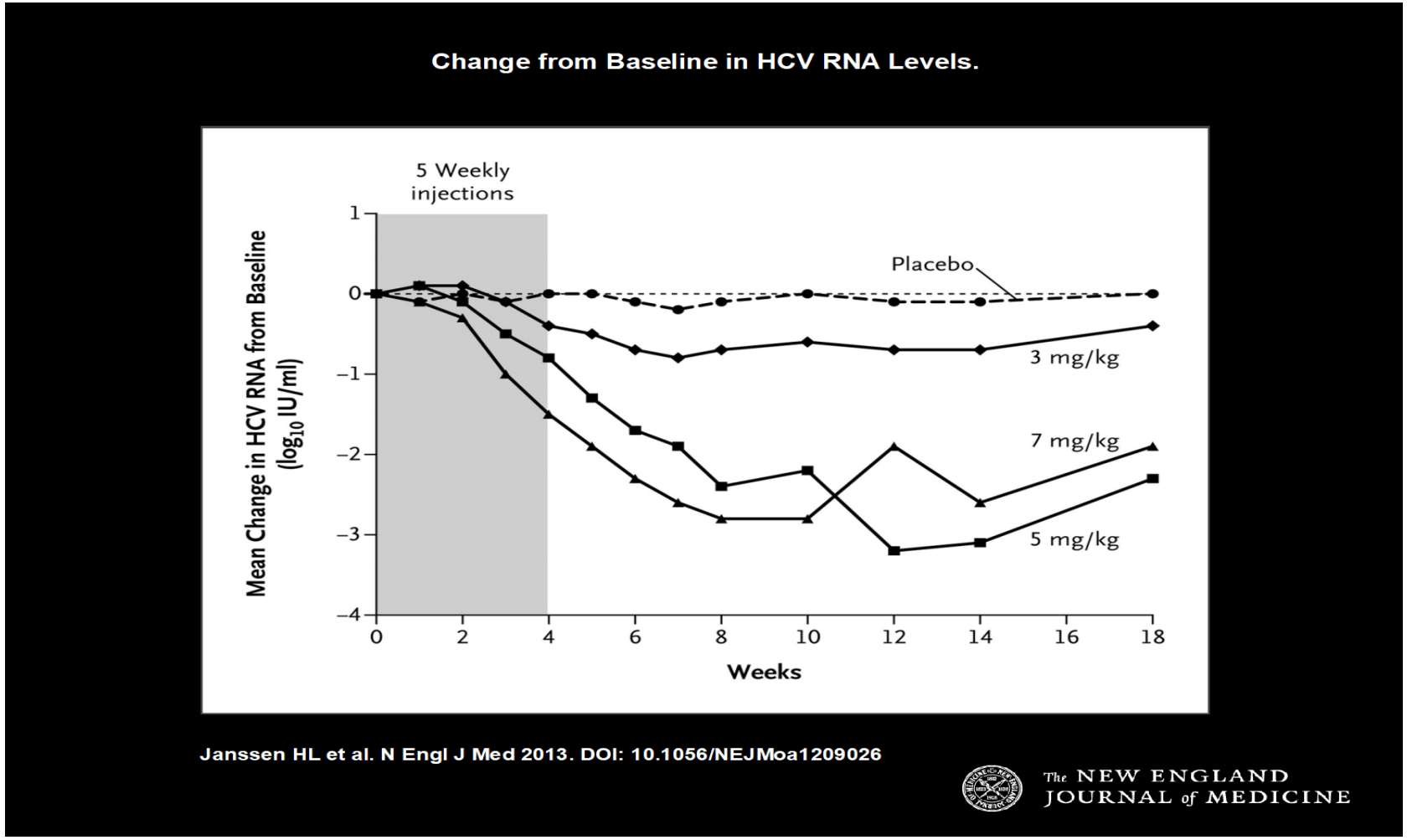
- RNA Mechanisms now in practice:

  - Steric blocking of start sites
  - RNAse H
  - RISC
  - Exon Skipping
  - Splice switching
  - Sequestration of splicing factors
  - mRNA correction
  - microRNA inhibitors and sponges
  - microRNA mimetics
  - Decoys
  - Synthetic mRNA
  - RNA Editing/ADAR

New Understanding RNA Mechanisms in Biology Critical in Developing New Drugs



Utilizing the Role of Human microRNA-122 to Target Hepatitis C Infection



RNA Editing: Altering properties of mRNAs to achieve novel biology

- mRNA can be altered before it's used to make proteins
- Some of the changes are big—large sections are cut out, and the remaining pieces are glued back together
- Other changes are small—sometimes, a single "A" gets converted into an "I" (functionally equivalent to a "G")
- Performed by group of enzymes called ADARs, which recognize specific sequences of RNA and makes those A-to-I changes

Benefits of RNA Editing vs. CRISPR DNA Editing

RNA Editing Benefits

- Reversible (Ethics & Safety)
- Endogenous machinery (Deliverability & regulatory)
- Non-viral delivery
- No protein expression required
- No strand breaking required
- Process used in eukaryotes

CRISPR DNA Editing Challenges

- Designed to promote integration of the molecule into the genome
- Target changes are permanent in the genome of somatic cells and possibly germ cells
- Off-target changes should they occur are permanent in the genome of somatic cells and possibly germ cells
- Delivery of guide RNAs
- Delivery of Cas9 protein or mRNAs encoding it
- Ramifications of DNA editing and off-target effects

New Understanding of RNA Editing in Nature: Octopuses, Squid, and Cuttlefish

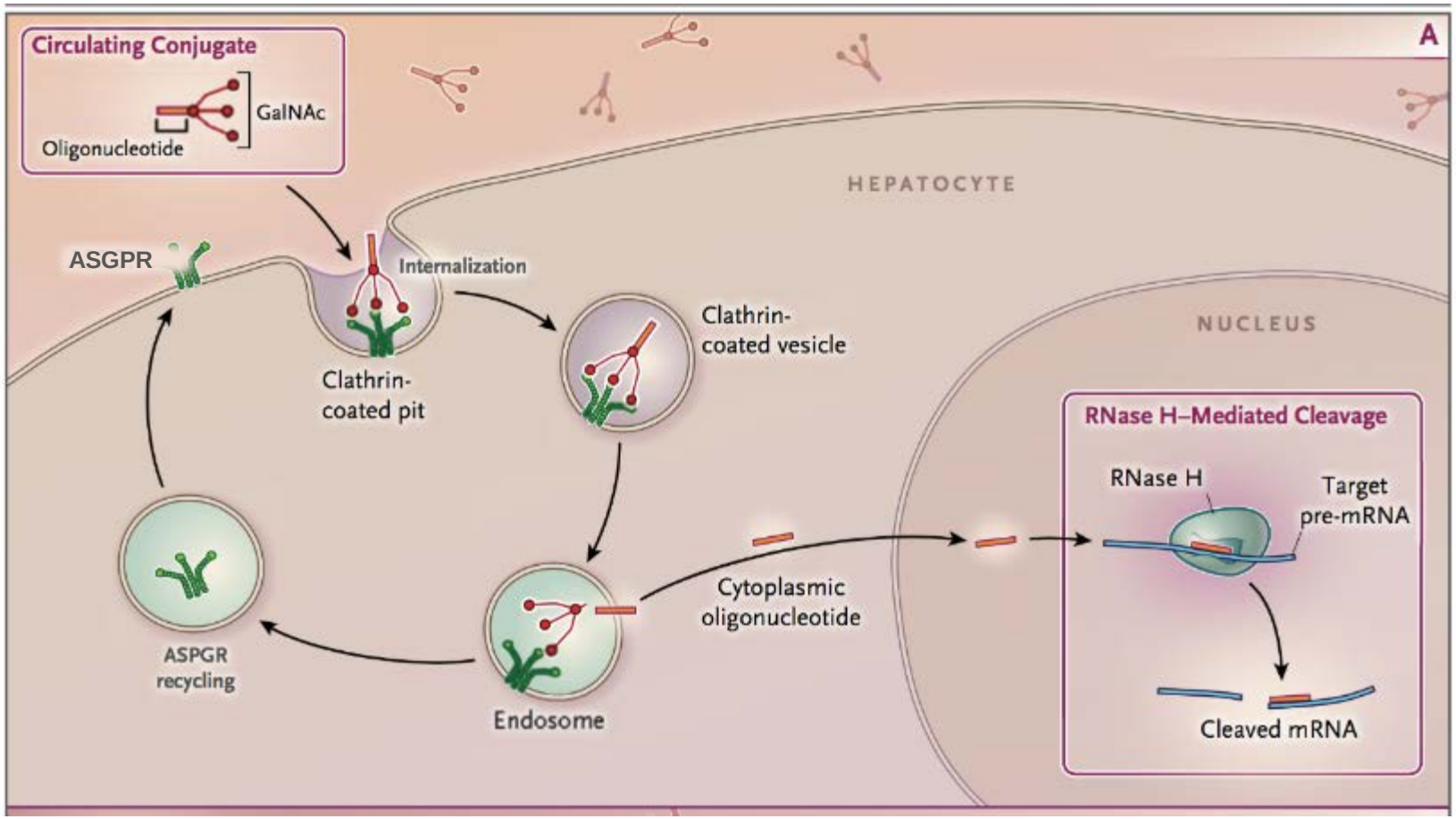
- Enzymatic “A” to “I” Conversions - Messenger RNA Massage
- Change the nature of proteins without altering the underlying DNA instructions.
- RNA editing is common in the neurons of cephalopods (100K ADAR sites)
- Editing may explain the plasticity of in brain octopus and some squid
- A to I recoding is extremely rare in mammals but the machinery is there. Only about 25 human genes are edited this way

From: Liscovitch-Brauer Cell 2017

Key Challenges in RNA-based Drug Development

- Delivery
- Delivery
- Delivery

Receptor-Mediated Uptake Hepatocytes for Delivery to Liver is Widely Used



From: Levin AA, NEJM 2017

Clinical Responses Demonstrate the Benefit of Targeted Delivery to Hepatocytes

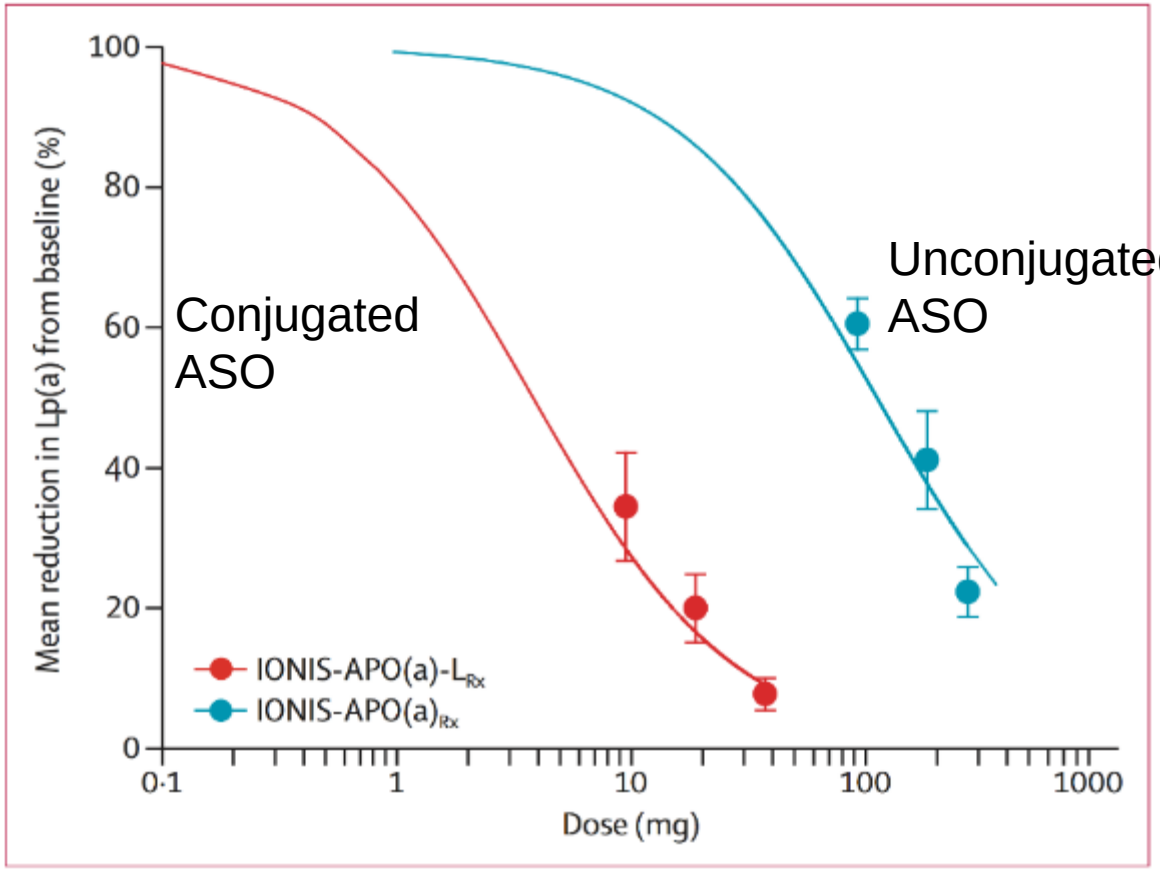
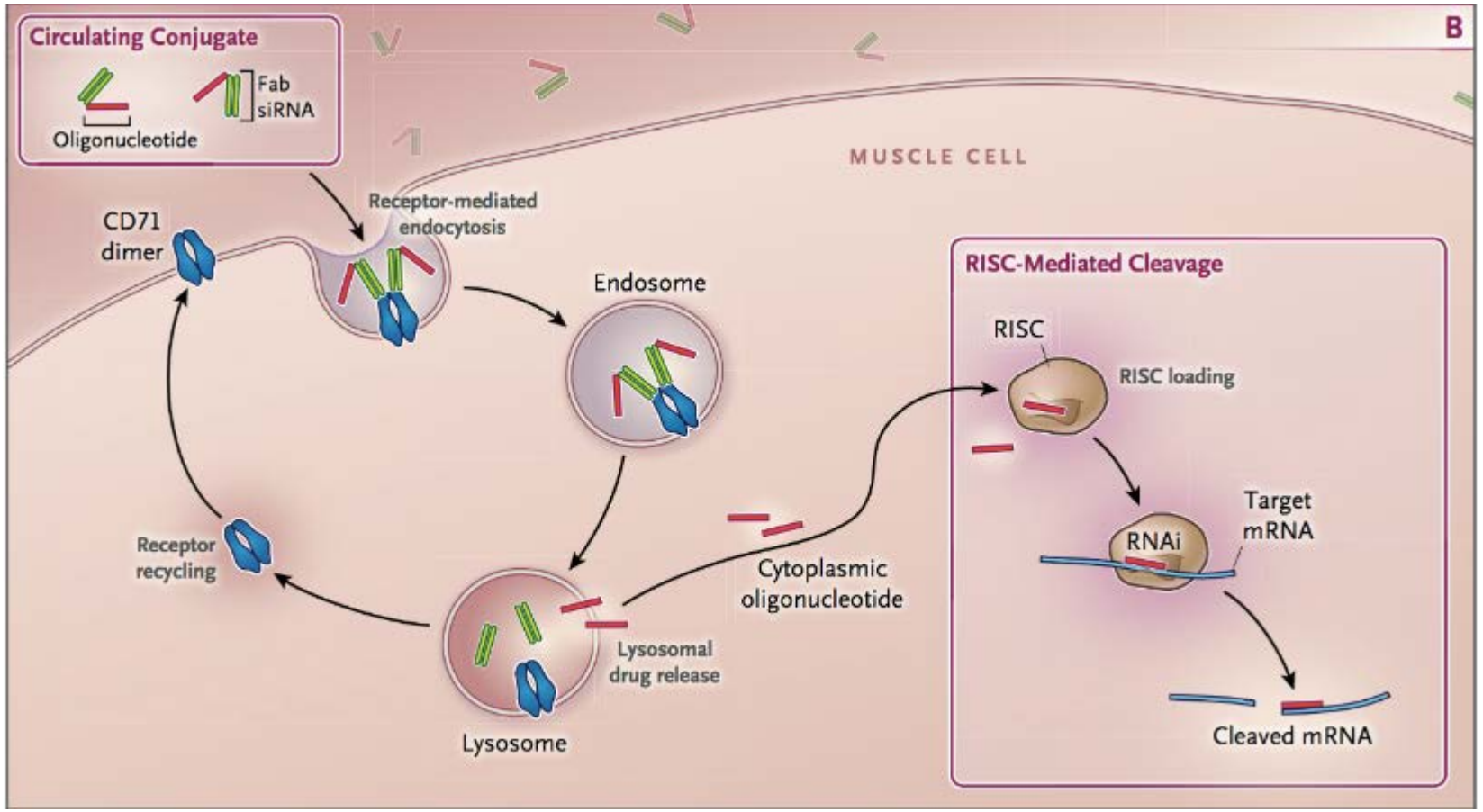


***Figure 4*: Comparison of dose–response curves of IONIS-APO(a)$_{Rx}$ and IONIS-APO(a)-L$_{rx}$ after 4 weeks of subcutaneous administration**
Error bars are SEM. The upper left side of the curve was extrapolated based on the curve fit of the data due to the fact that lower doses were not tested.

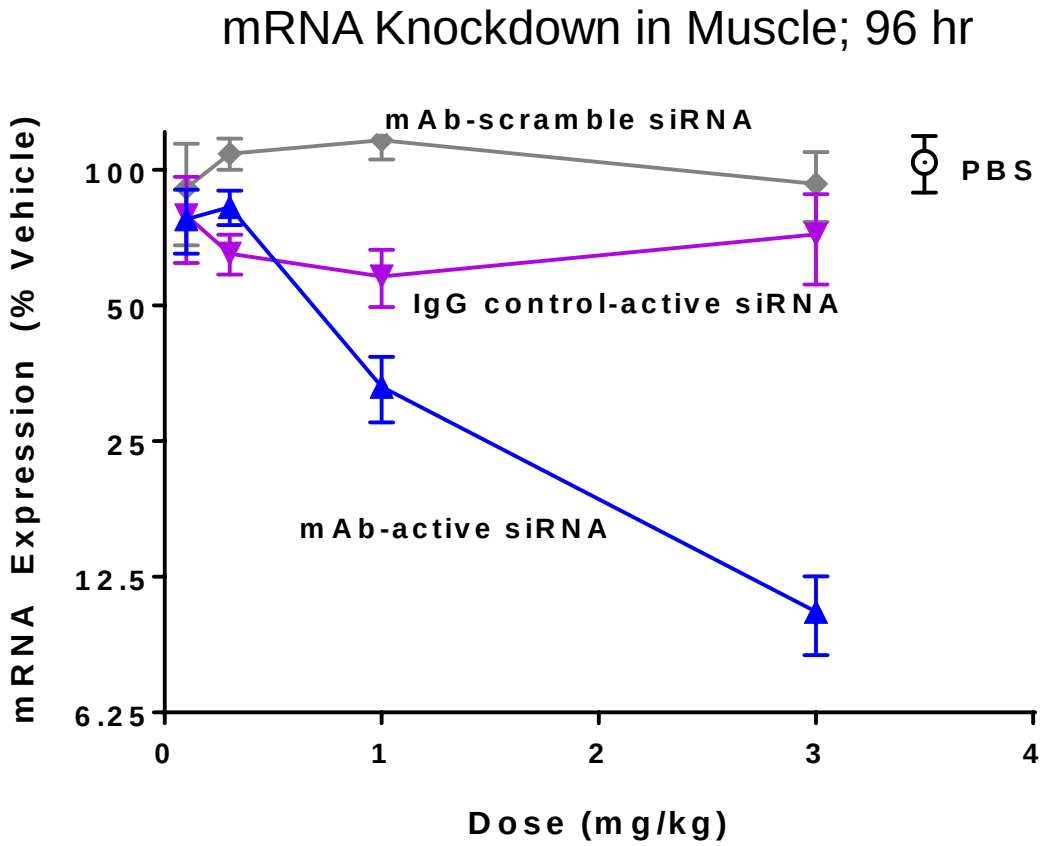
From: Viney et al Lancet 2016c

Utilizing Other Cell Surface Receptors to Deliver Oligonucleotide Payloads



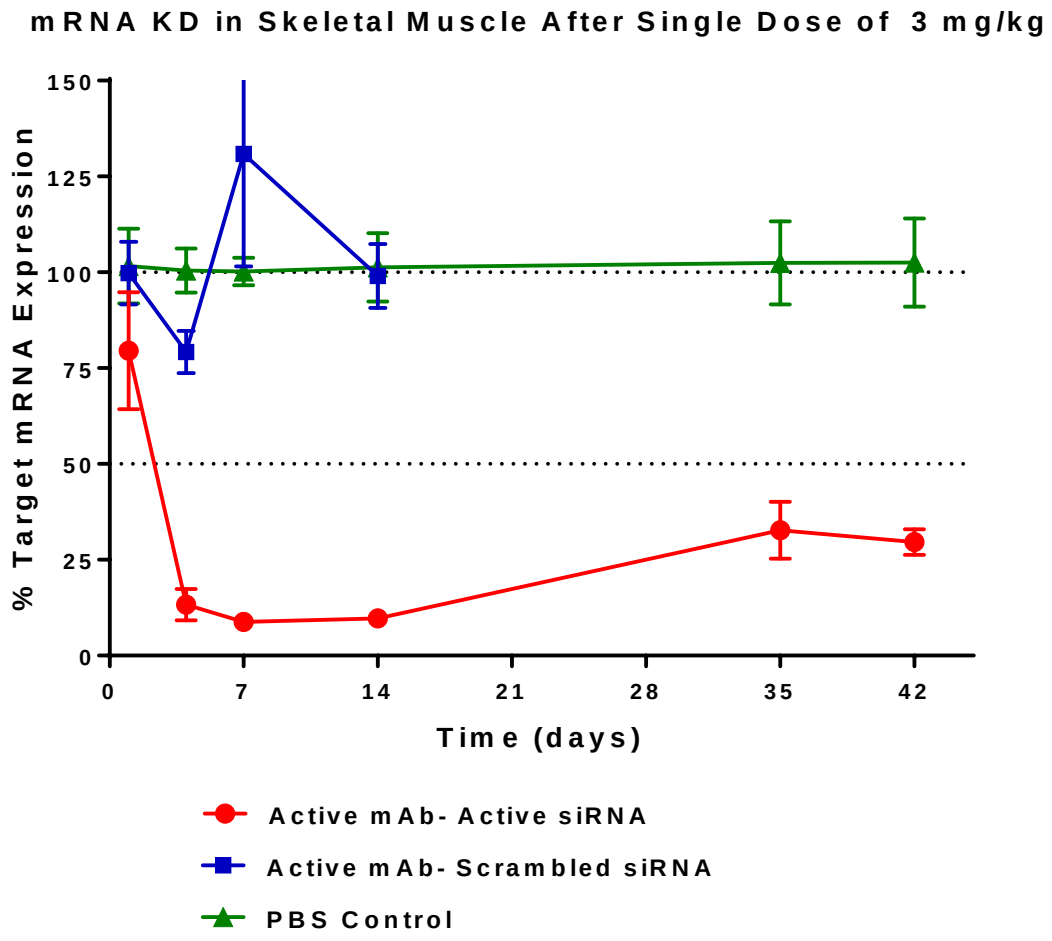
From: Levin AA, NEJM 2017

mAb-siRNA Conjugates Produce Reductions in Target Gene Expression in Muscle in Mice

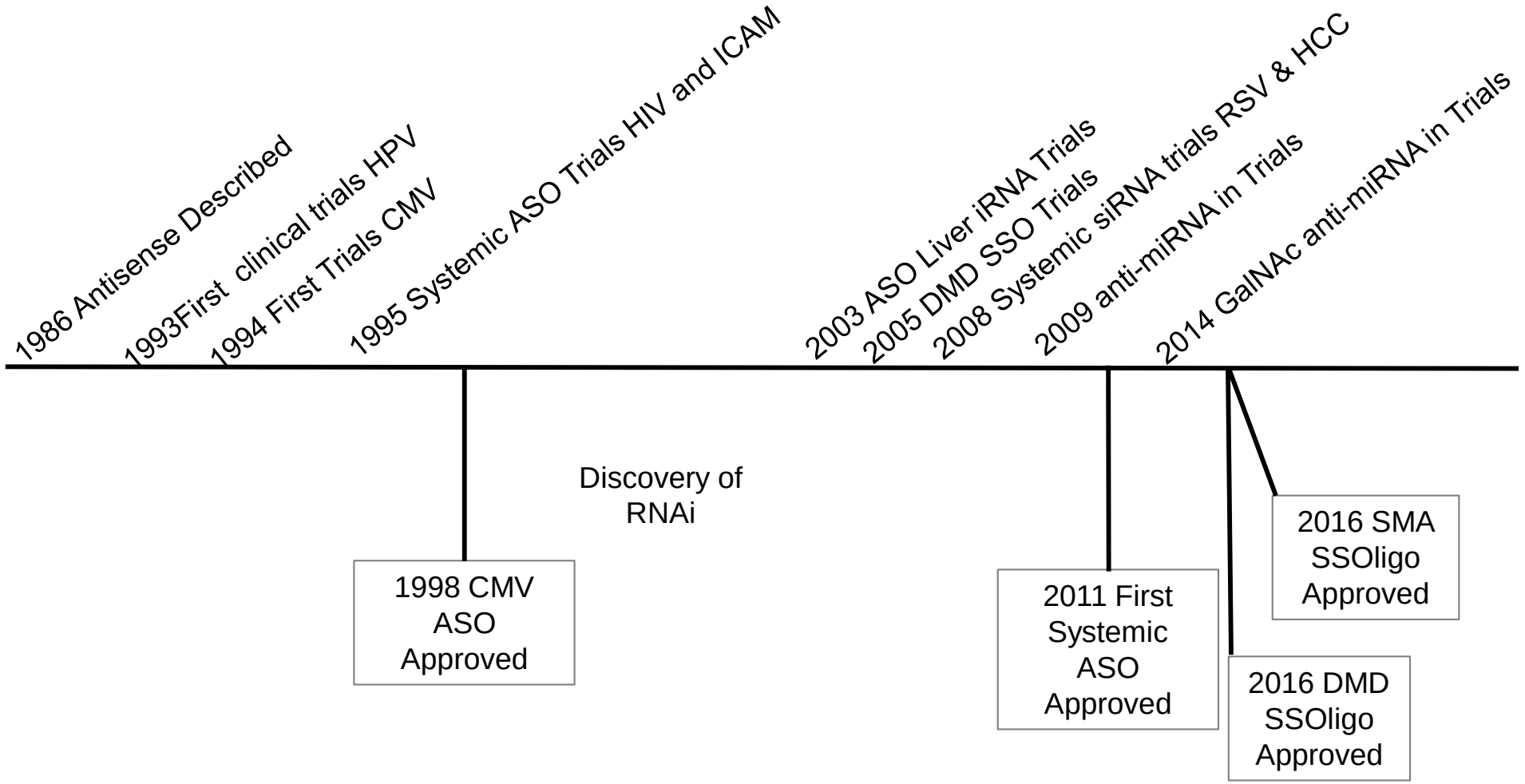


- Single injection of **3 mg/kg** dose produced **>90%** knockdown of target gene at 96 hrs

Exploiting Other Cell Surface Receptors to Deliver Oligonucleotide Payloads: Long Lived Activity



Timeline of Key RNA-based Drug (Antisense Oligonucleotide) Development



Innovation: ProQR Uniquely Positioned to Develop RNA-based Treatments

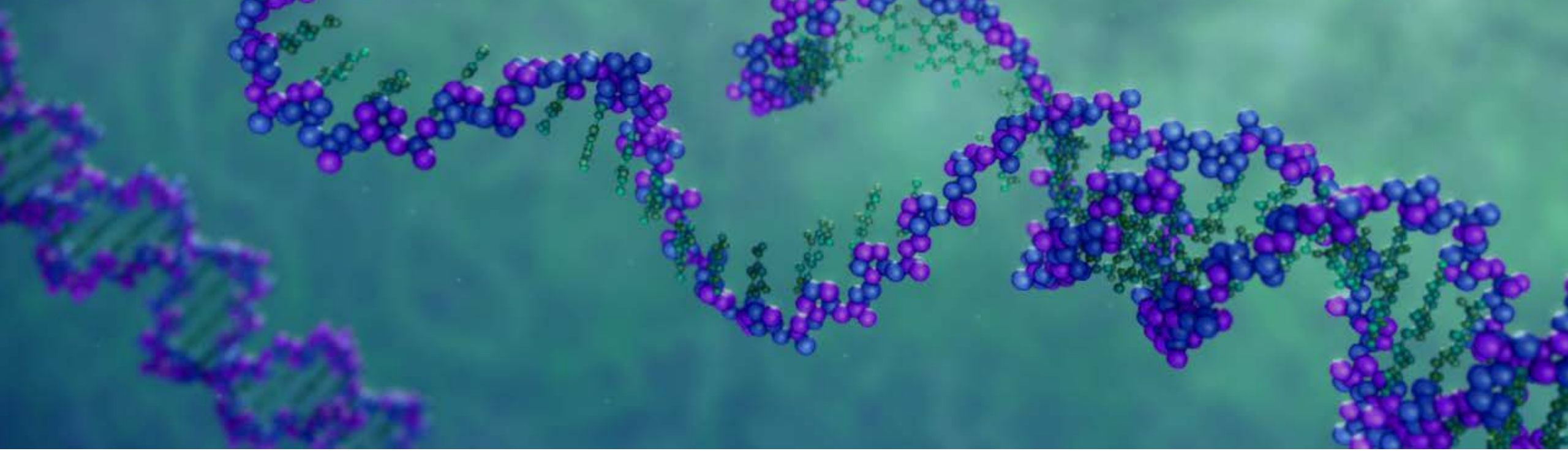
- ProQR utilizing local delivery
  - QR-010 for CF
  - QR-110 for LCA
  - QR-313 for EB
  - QRX-421 and QRX-411 for Ushers
- Axiomer (A to I Editing) a nu wave

- ProQR embraces the totality of RNA biology and is exploiting multiple mechanism of action and multiple regulatory processes

Why Be Optimistic about RNA-Based Therapeutics

- The most direct application of genomic revolution for design of medicines
- Nature uses RNA for modulation of gene expression, anti-viral activity and creating plasticity in responses
- Ample evidence for activity of RNA treatment modalities in animal models and man
- Path for development is now established with PK/Tox/CMC issues understood
- RNA-targeting drugs have growing importance as we come to greater understand the RNA world
- RNA-targeting drugs are poised to exploit this understanding

Thank you



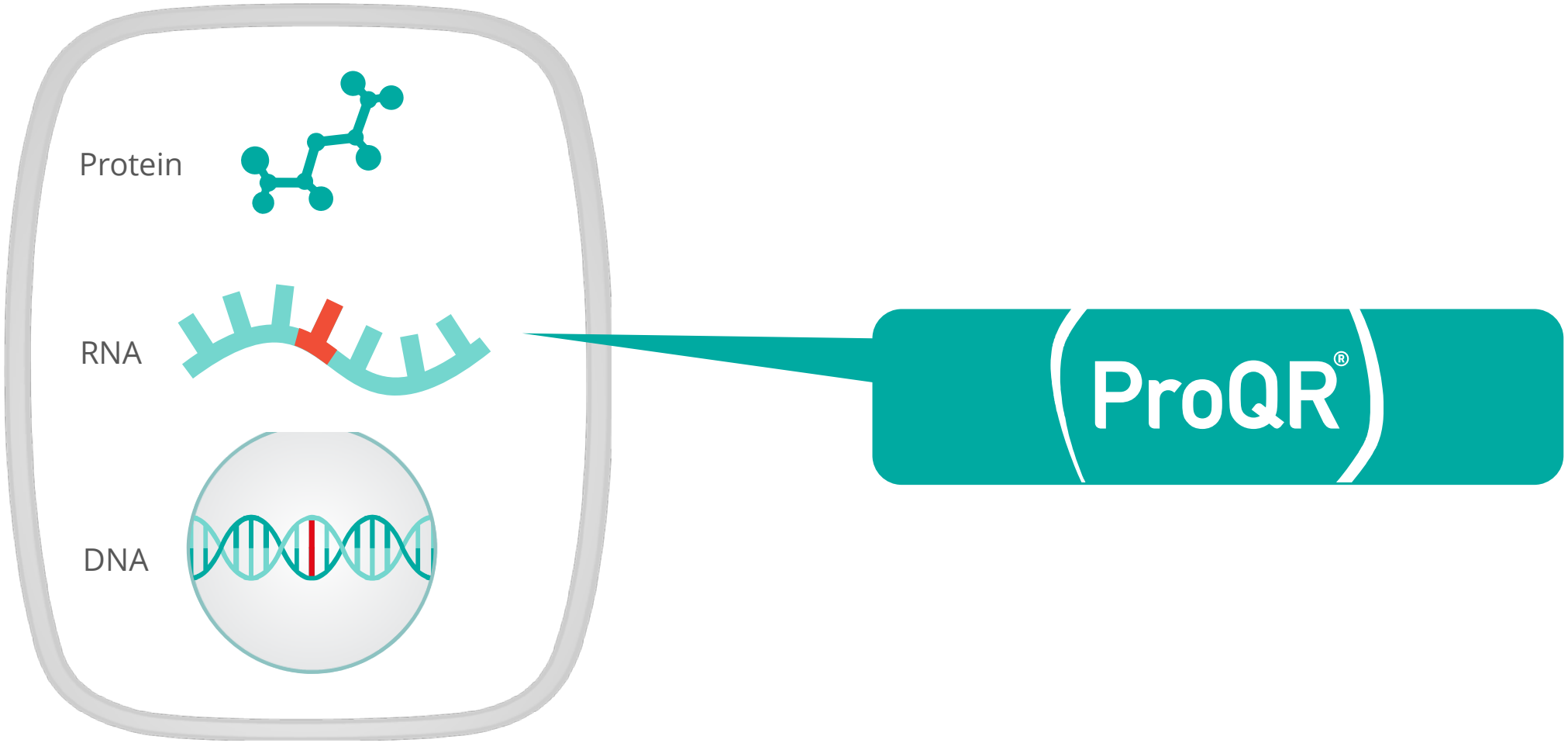
Innovation

ProQR's pipeline filler

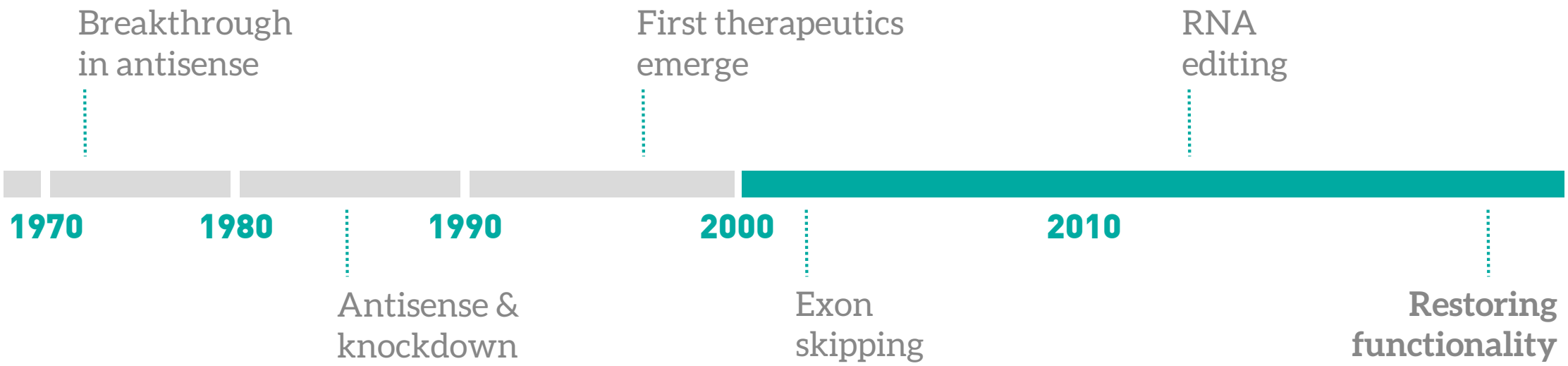
Presenter: **Gerard Platenburg**

Innovation platform

Targeting genetic disorders at the RNA



RNA space


Breakthrough in antisense
First therapeutics emerge
RNA editing
1970
1980
1990
2000
2010
Antisense & knockdown
Exon skipping
Restoring functionality

Innovation at the core

Targeting severe genetic diseases

RNA modulation to correct genetic mutations

Local delivery

Diversified pipeline

Efficient discovery engine to development

- > 8000 genetic diseases known
- Majority single gene diseases
- Causality mostly known
- Limited treatment options
- Viable commercial strategy
- Restoring protein function is key

Innovation at the core

Targeting severe genetic diseases

RNA modulation to correct genetic mutations

Local delivery

Diversified pipeline

Efficient discovery engine to development

- Altering protein function
- Restoring protein function
- Knock-down protein function
- Knock-down protein expression
- Protein modulation:
  - Homeodomain removal
  - Restoring mutation
- Modulating mRNA translation into a protein

Innovation at the core

- Targeting severe genetic diseases
- RNA modulation to correct genetic mutations
- Local delivery
- Diversified pipeline
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Innovation at the core

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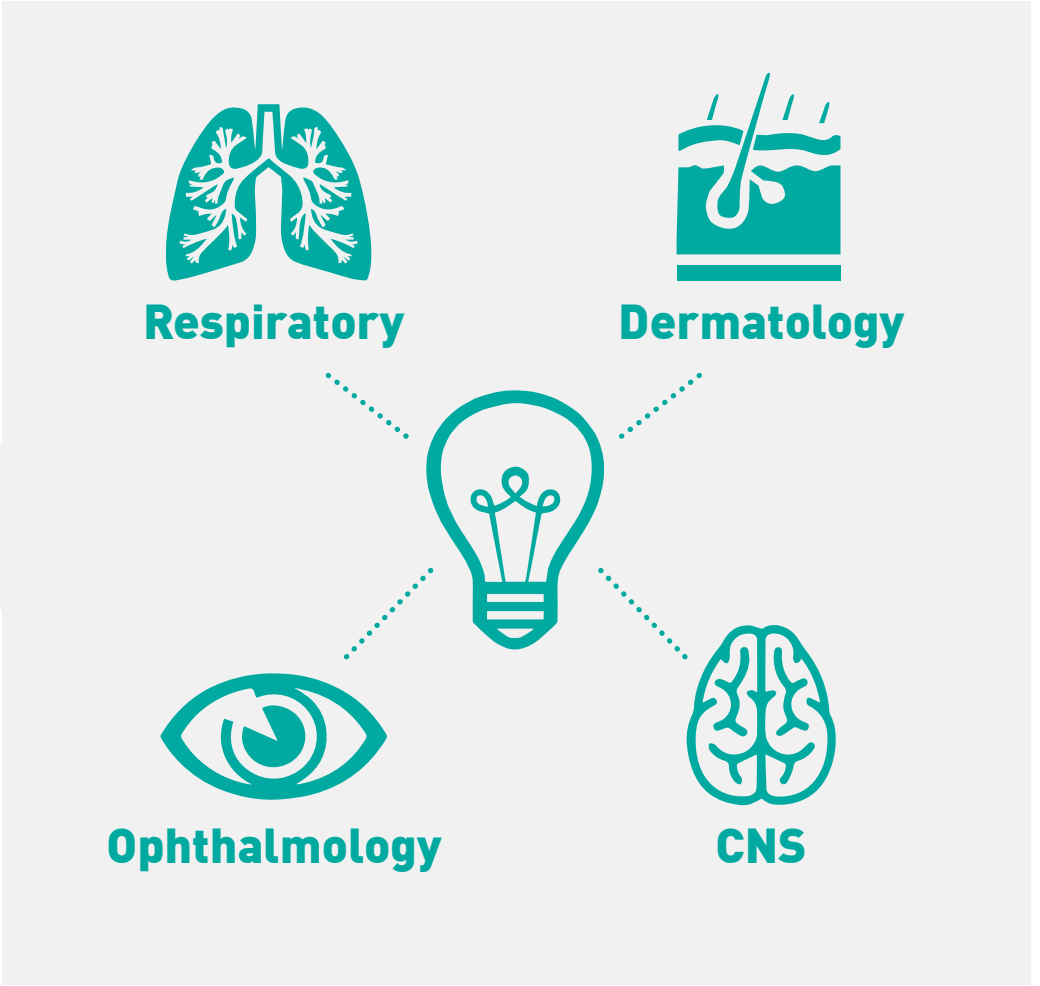

Innovation at the core

- Targeting severe genetic diseases
- RNA modulation to correct genetic mutations
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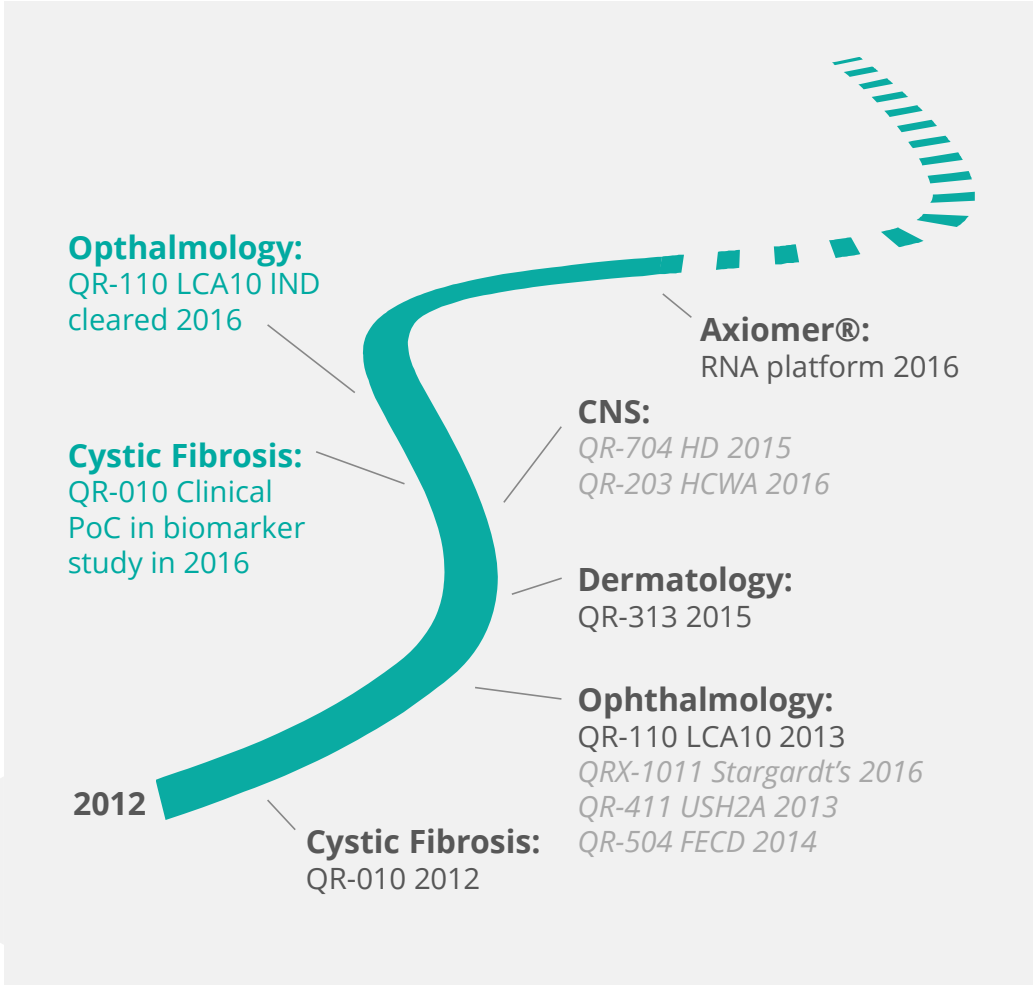
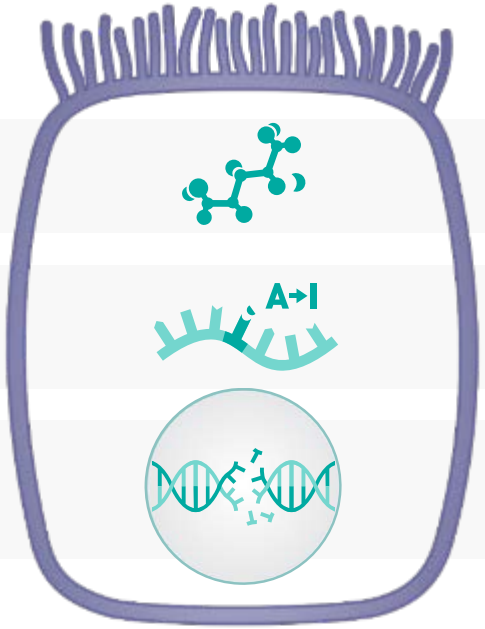


Axiomer® technology

Editing OligoNucleotides (EONs)
A new class of medicines

Axiomer® – "RNA editing"



Protein

RNA — ADAR – RNA editing

DNA — CRISPR – DNA editing

	ADAR
Reversible (Ethics & Safety)	√
Endogenous machinery (Deliverability & regulatory)	√
Non-viral delivery	√
No protein expression required	√
No strand breaking required	√
Applicability	A>I (G)

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

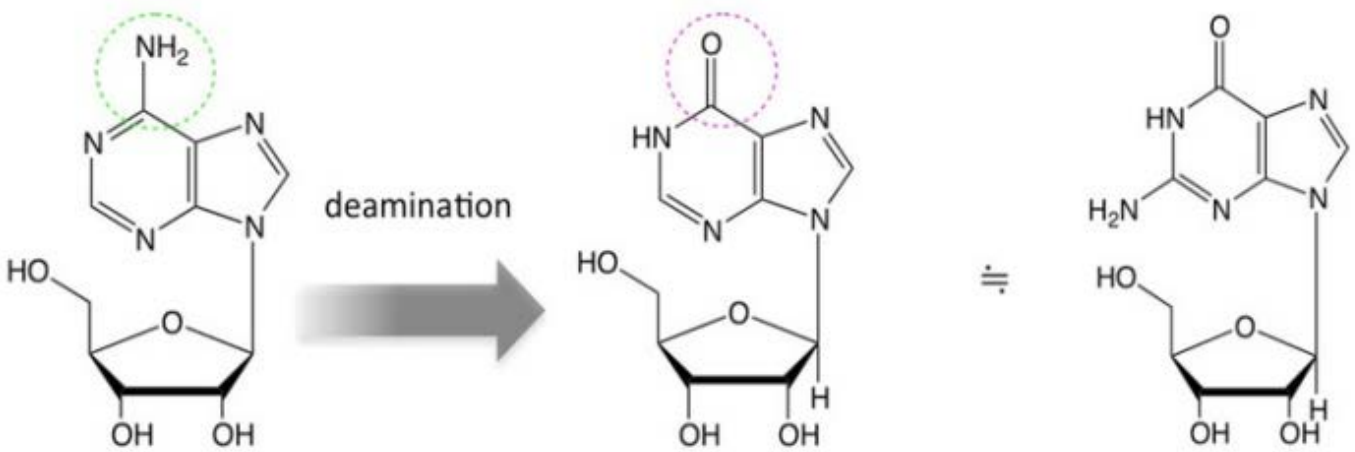
Brings clinical applicability of "editing" in reach

IP fully owned ProQR far ahead of competition

In-vitro PoC established in multiple disease models

ADARs deaminate adenosine in dsRNA

Adenosine Deaminase Acting on RNA



Adenosine **Inosine** **Guanosine**

- Inosine is synonymous with Guanosine
- ADARs are expressed in the cells of most eukaryotes
- A to I editing is very common: > 10^6 targets in the human transcriptome
- RNA editing alters gene expression and recodes proteins

ADARs natural substrate features

ADAR naturally binds and edits adenosines in dsRNA structures

- Imperfect stems
- Bulges or loops

Natural ADAR editing can be specific or promiscuous

- Structural features of the substrate are important
- Nucleotides neighboring the target Adenosine provide context

Sequence as such not important

EONs recruit resident ADAR to target

Can we recruit ADAR to edit therapeutic targets

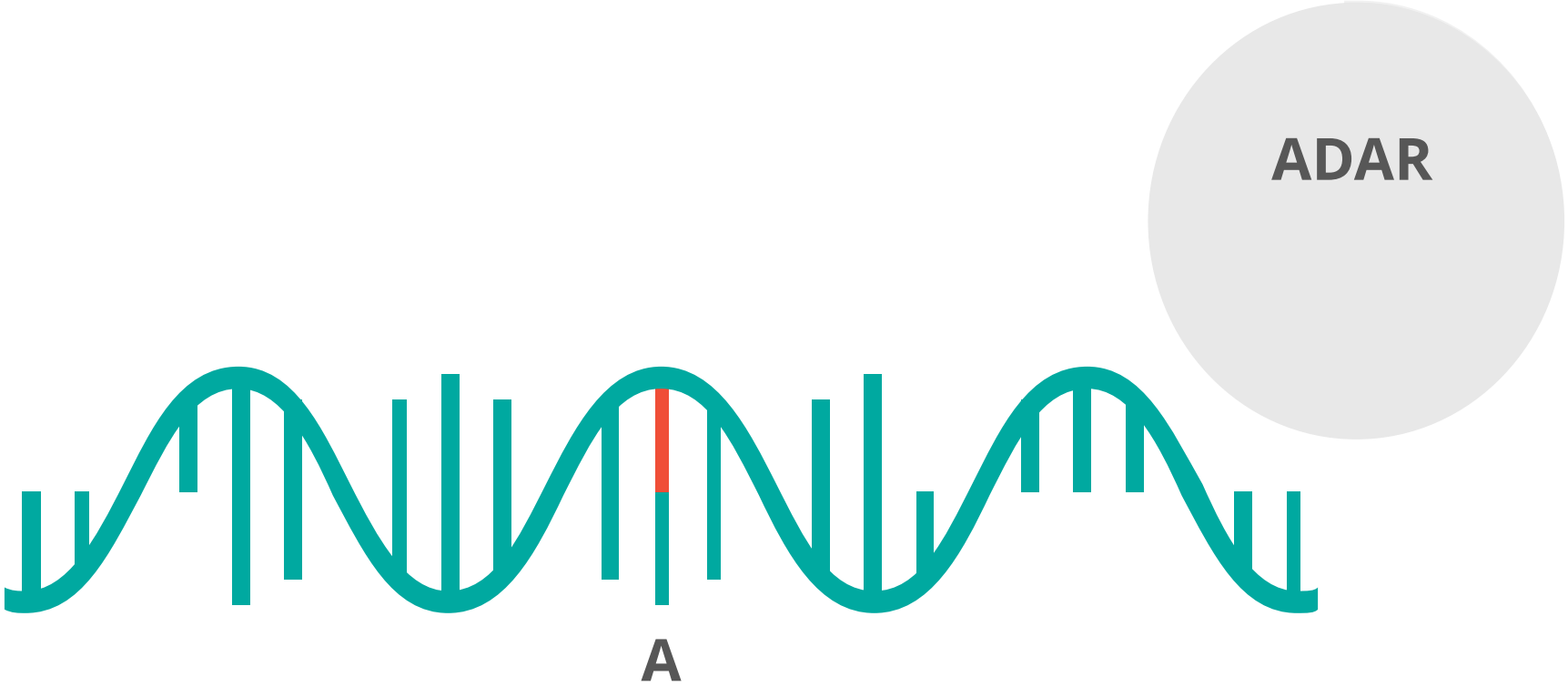
Key Questions	
Can we recruit ADAR to edit **any** target transcript ?	✓
Can we make it **specific** for the target adenosine ?	✓
Is there **sufficient** *ADAR* in the cell ?	✓
Can we create a **single component** EON based therapy ?	✓
Can we postulate generic EON **design rules** ?	✓
Can we overcome editing **context preference** ?	✓
Are ADARs present in **therapeutically relevant** mouse and human tissues ?	✓

Rationale of Axiomer® EON design

- Target finding by Watson-Crick base pairing
- Mimic dsRNA structures of natural substrates (e.g. GRIA2)
- Recruiting ADARs to bind the mimicked structures
- Allowing or promoting flipping of the target adenosine
- Promoting editing of the target adenosine
- Preventing editing of non-target adenosines
- Chemical modifications compatible with editing
- Drug-like properties

ADAR recruited by EON

Adenosine deaminases acting on RNA



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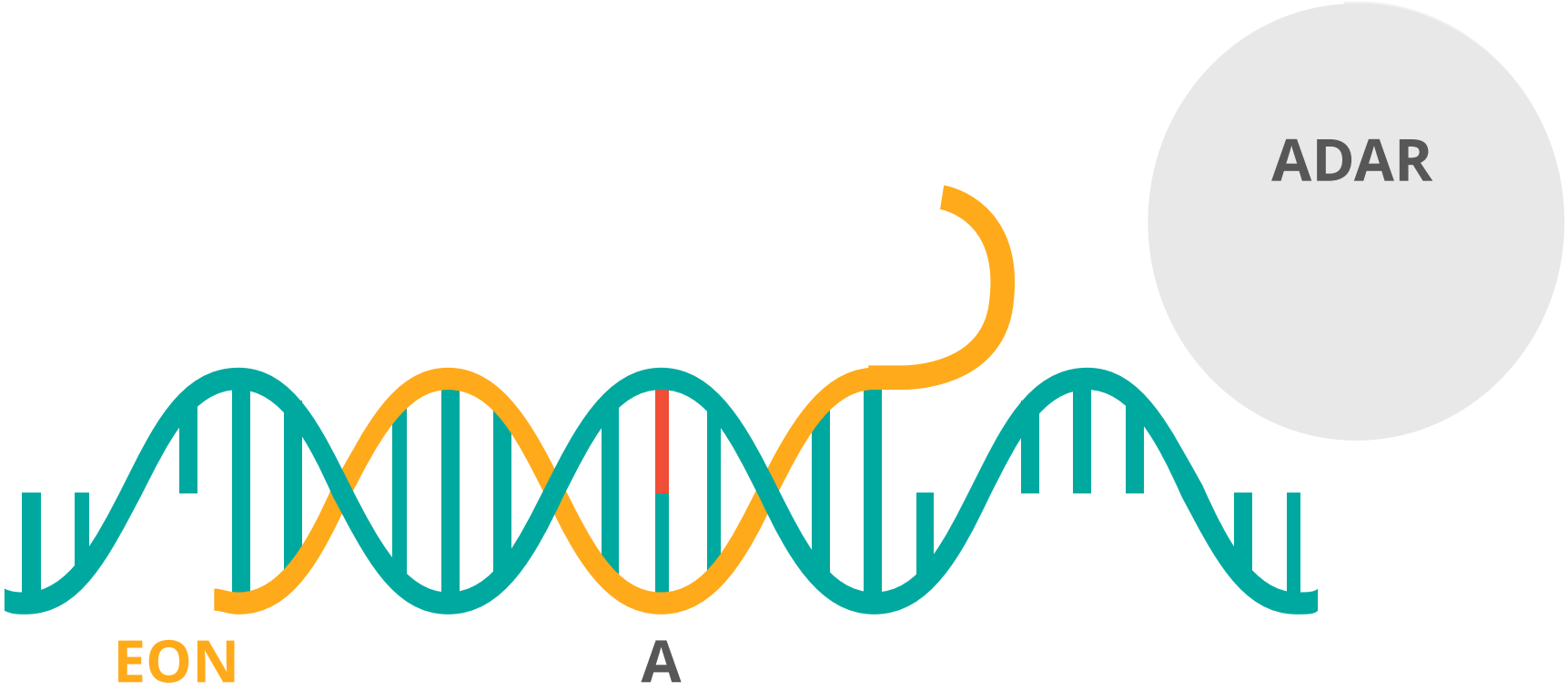

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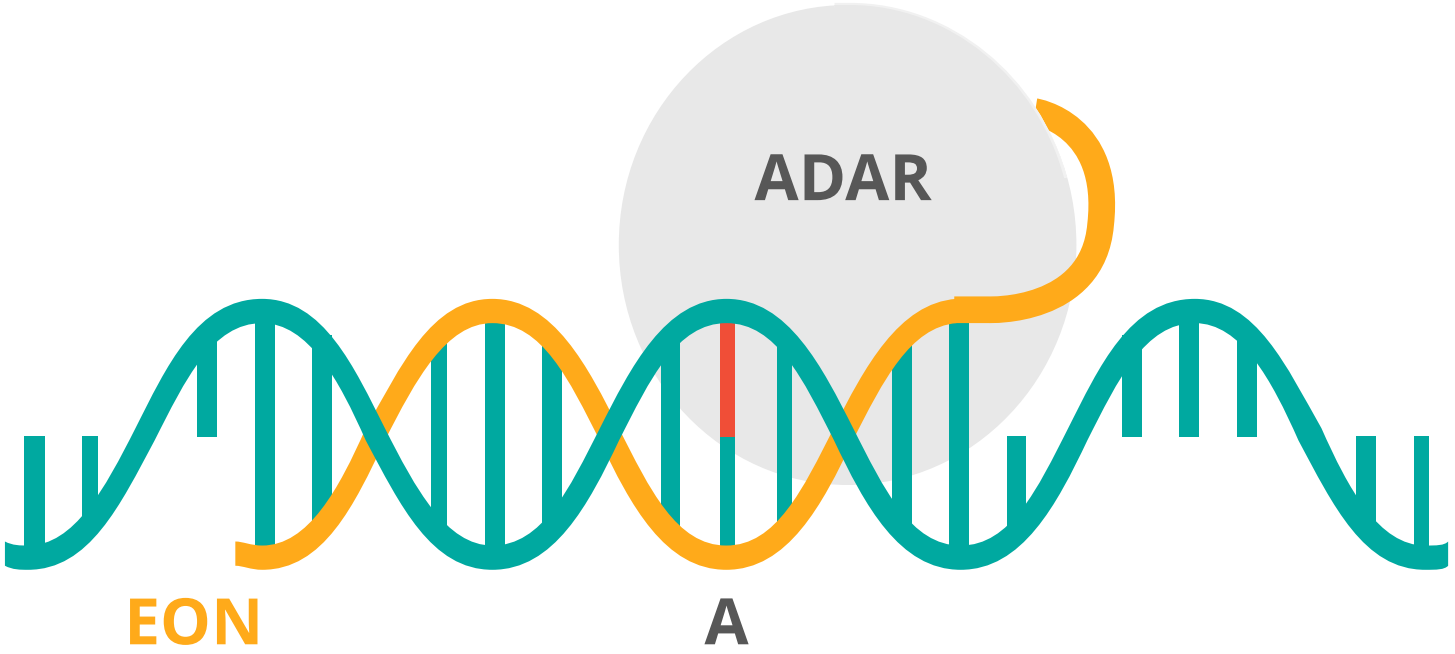


ADAR recruited by EON

Adenosine deaminases acting on RNA

ADAR recruited by EON

Adenosine deaminases acting on RNA

Widely applicable to:

- (Premature) stopcodon / UTR's
- (Cryptic) splice sites
- Intronic and Exonic mutations
- Amino acid substitutions (K, R, H, D, E, Q, N, Y, S, T, I, M)
- miRNA modulation

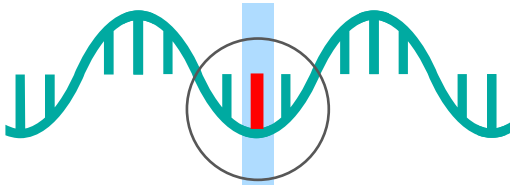
EONs can restore ORFs

In vitro Proof of Concept in GFP cell model

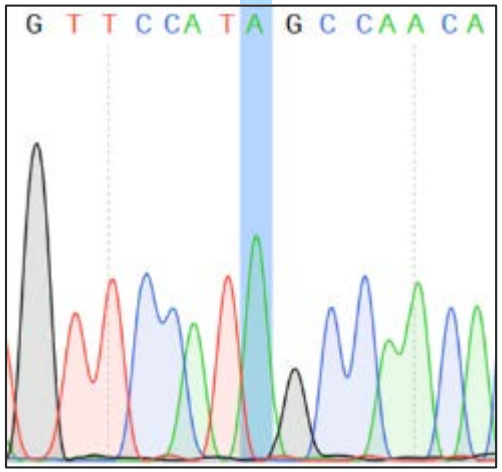
Wildtype

UGG

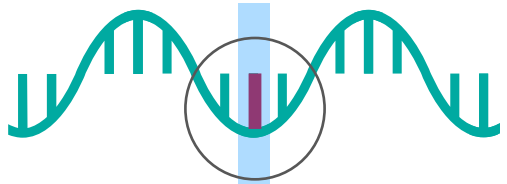
Mutation



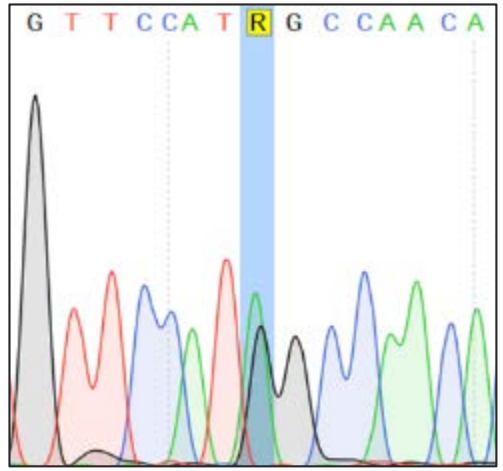
UAG



Mutation treated with EON



UIG



GFP model

- Target RNA with stop mutation
- EON guide strand to recruit ADAR
- Efficacy by Sanger sequencing

EON treatment results in 50% A>I editing
I is translated as a G

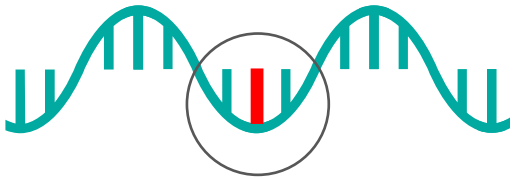
EONs can restore ORFs

In vitro Proof of Concept in GFP cell model

Wildtype

UGG

Mutation



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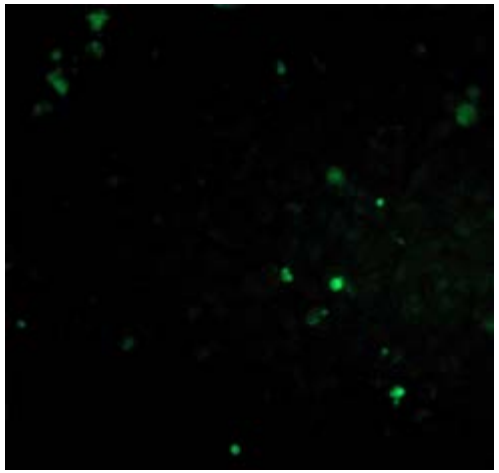
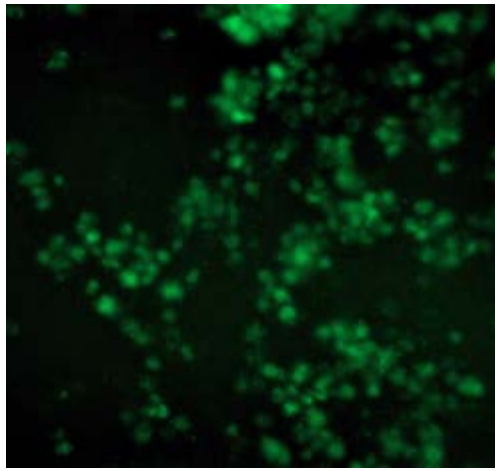


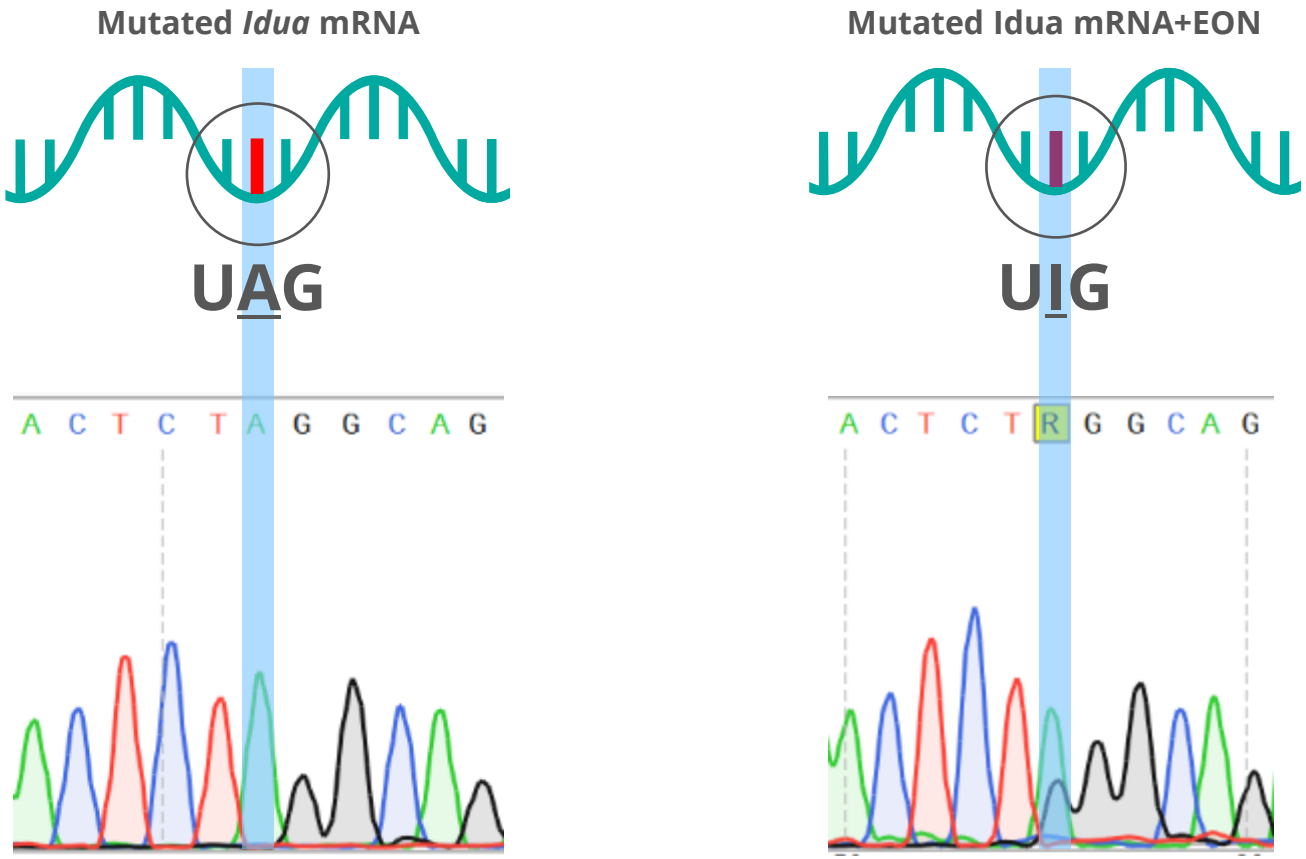


EON treatment results in 50% A>I editing
I is translated as a G

EONs can restore ORF in Hurler model

Hurler model

- Mucopolysaccharidosis type I
- Iduronidase deficiency
- Target RNA with stop mutation
- EON guide strand to recruit ADAR
- Efficacy by Sanger sequencing



EON treatment results in ~25% A>I editing

EONs can restore ORF in Hurler model

Hurler model

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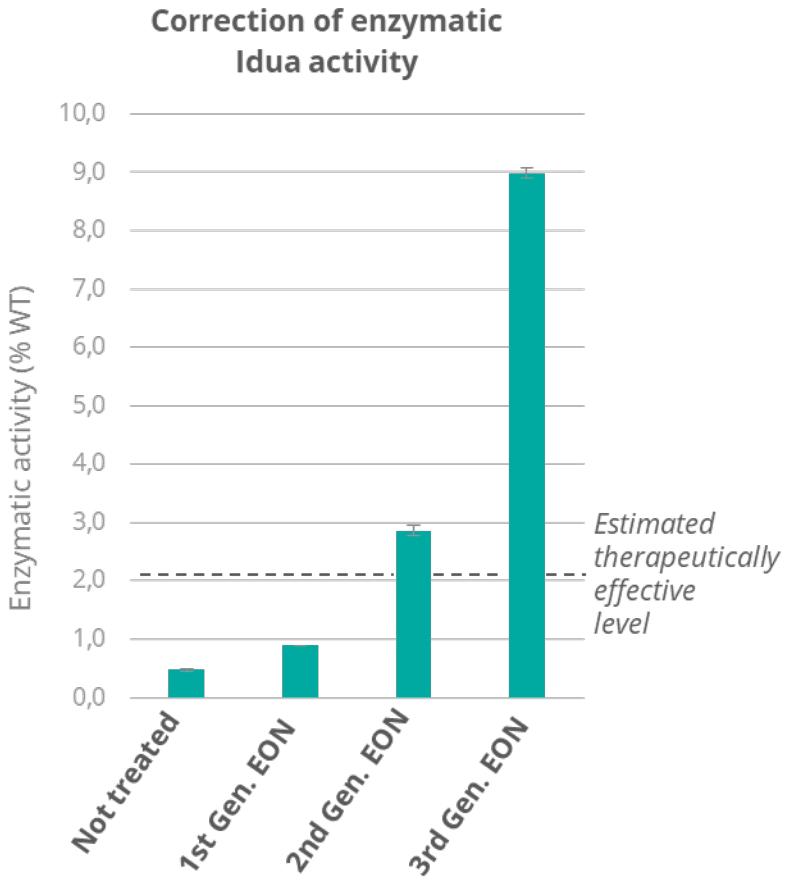
- Iduronidase deficiency
- Target RNA with stop mutation
- EON guide strand to recruit ADAR
- Efficacy by Sanger sequencing



EON treatment results in functional Idua

Axiomer® EON targeted RNA editing

Gene	Disease
IDUA	Hurler syndrome
Serpina1	α1-antitrypsin deficiency
PINK1	Parkinson's disease
FV Leiden	Factor V Leiden deficiency
CFTR	Cystic fibrosis
GFP, b-actin, Snrpa, GAPDH, GPI, GUSP, RAB7A, VCP	Models

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Applicable to >20,000 disease-causing mutations

Similar capabilities as CRISPR, without the key risks

Brings clinical applicability of "editing" in reach

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Axiomer® next steps and strategy

Next steps

- Complete optimization of PoC in vitro and in vivo in 2017

Strategy

- >20,000 disease causing mutations are G>A mutations
- Axiomer® platform technology can yield large number of new medicines for currently untreatable diseases
- ProQR will pursue an active business development strategy to develop the platform to its full potential and generate non-dilutive funding

ProQR®

ProQR R&D DAY

JUNE 15, 2017, NEW YORK

ProQR®

IT'S IN OUR RNA