# Therapies for Usher Syndrome

## *Update to Families*

*Gwenaëlle Géléoc, PhD*
Assistant Professor

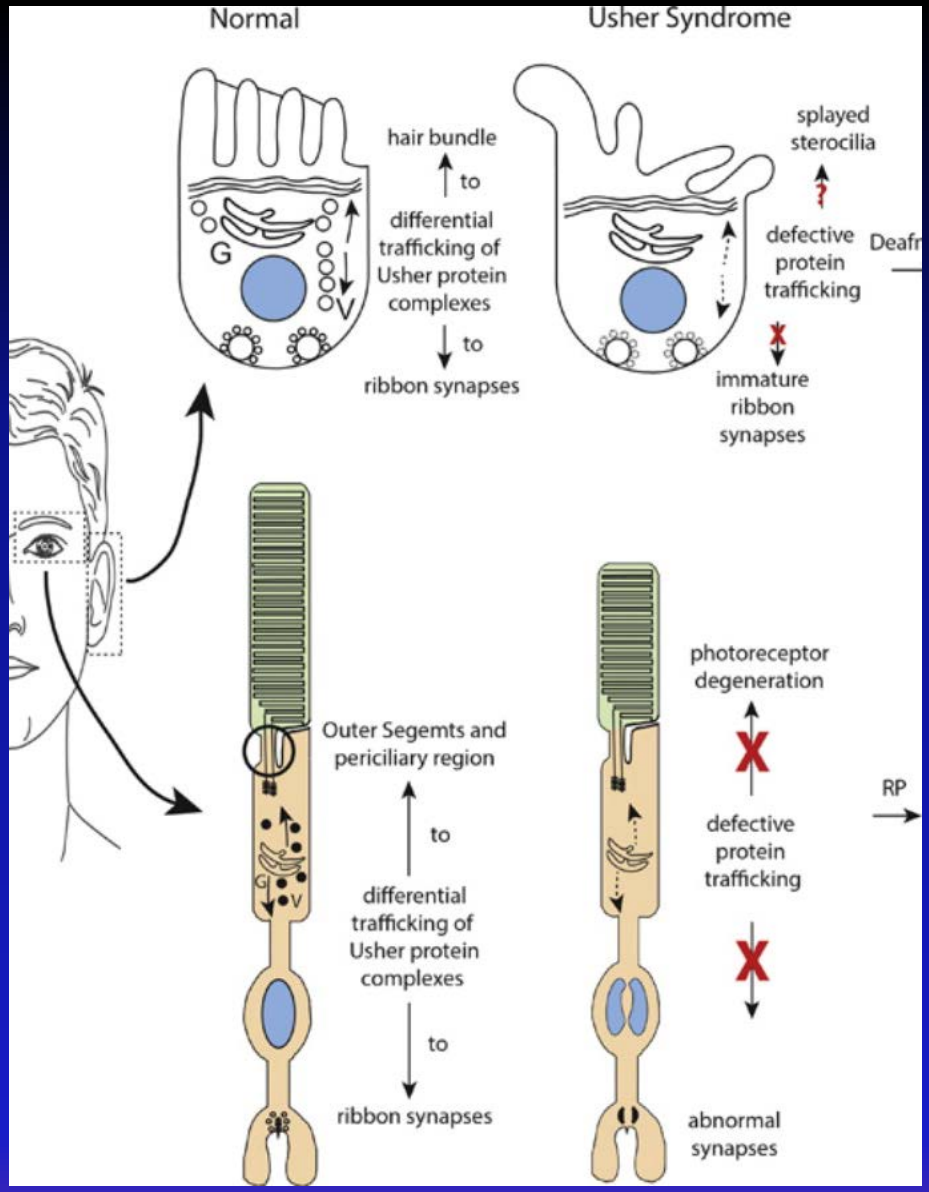
BOSTON CHILDREN'S HOSPITAL

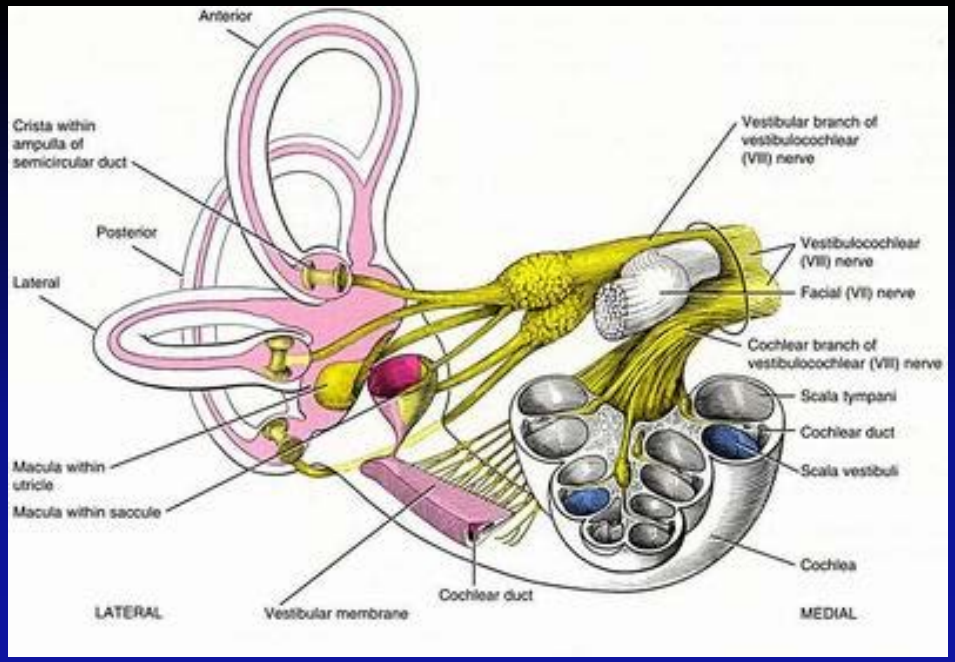
HARVARD MEDICAL SCHOOL

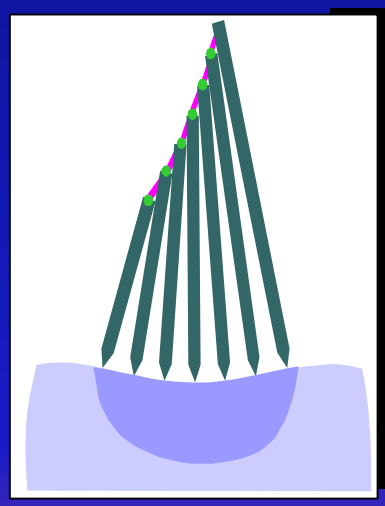
**#USH2018**

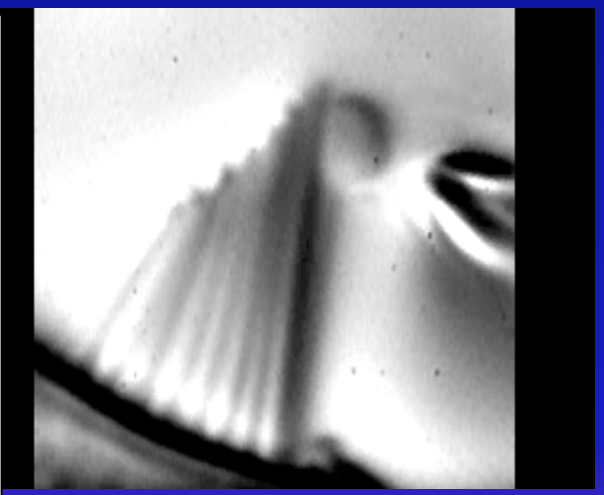
usher syndrome society

# Usher Syndrome



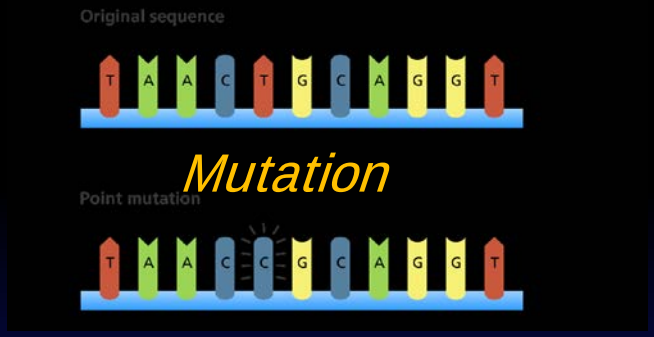



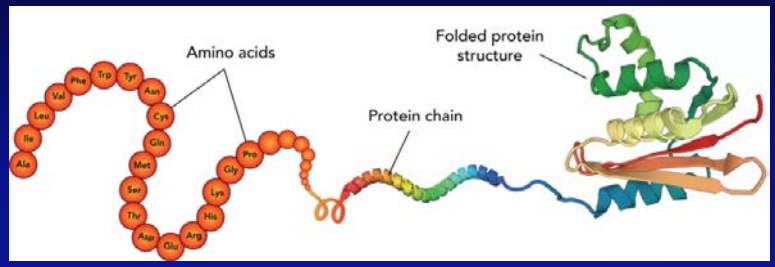


*Cosgrove and Zallocchi, 2014, IJBCB*

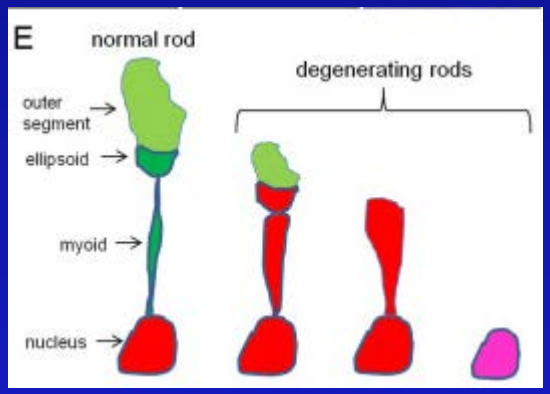
Gene

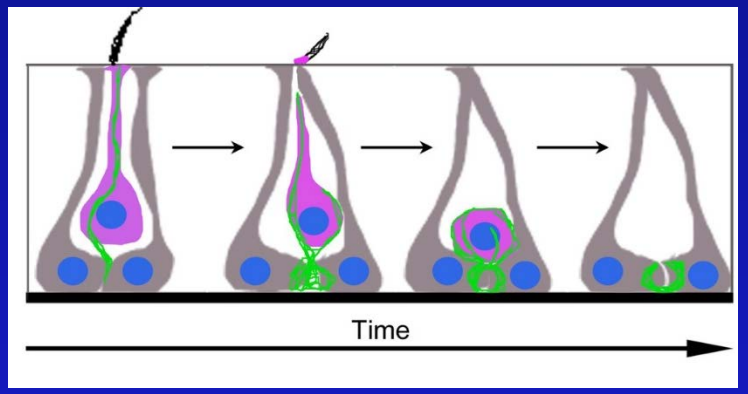



Protein




Cell



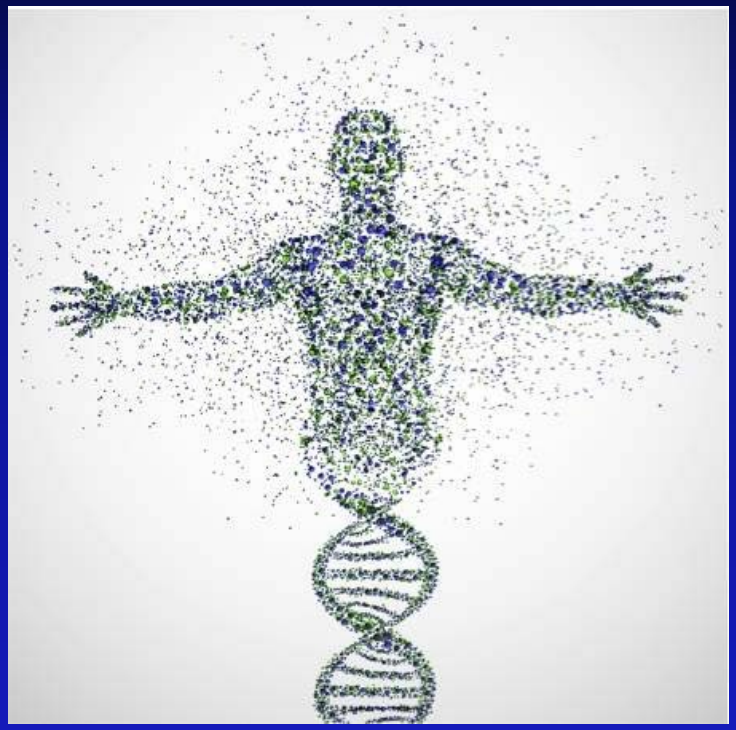




Organ

# Therapies for Usher Syndrome

**Gene augmentation therapy**

**Small molecules & pharmacology**



**Gene editing**

**Correction of translation**

# Scientific meeting

## Gene augmentation therapy

**Alberto Auricchio**, Naples, IT
"Dual AAV vectors for gene therapy of USHIB retinitis pigmentosa "

## Gene editing

**Carla Fuster García**, Valencia, ES (# 34)
"USH2A Gene Editing Using the CRISPR System"

## Antisense and translational read-through therapy

**Erwin van Wijk**, Nijmegen, NL
"Antisense oligonucleotides for the treatment of Usher syndrome caused by splice site mutations"

**Jennifer J. Lentz**, New Orleans, US (# 37)
"Antisense Therapy Rescues Hearing and Vision in Usher syndrome"

**Kerstin Nagel-Wolfrum**, JGU Mainz, DE
"Translational read-through as therapy for Usher syndrome caused by nonsense mutations"

# Scientific meeting

## Small molecules and pharmacology

**Yoshikazu Imanishi**, Cleveland, US
"A small molecule mitigates hearing loss in a mouse model of Usher syndrome III"

**Alaa Koleilat**, Rochester, MN, US (# 36)
"Development of the first pharmacotherapy for the treatment of Usher Type I due to variants in MYO7A"

## Stem cells

**Mike Cheetham**, London, UK
"Retinal organoids as disease models"

**Anai Gonzalez Cordero**, London, UK (# 31)
"Using hiPSC-derived retinal organoids to model Ush2a pathophysiology"

# **December 2017**: First retinal gene therapy is approved

*Dr. Jean Bennett*


On December 19, 2017, the U.S. Food and Drug Administration approved a new gene therapy (AAV2-hRPE65v2Luxturna), manufactured by Spark Therapeutics in Philadelphia.

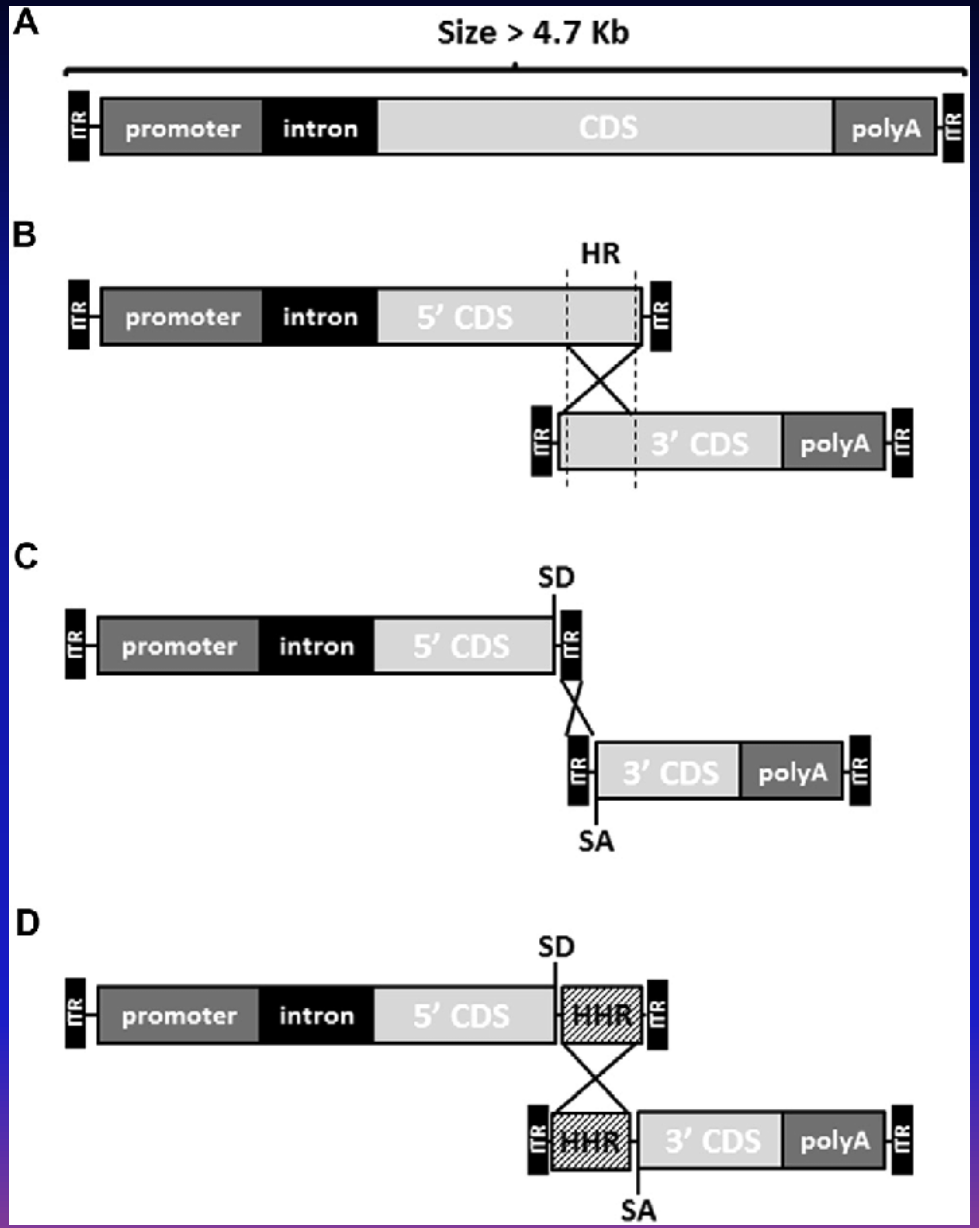
Luxturna is the first gene therapy approved in the United States that's directly administered into the eye, targeting diseases caused by mutations in the gene RPE65. Mutations in this gene can produce Leber's congenital amaurosis or retinitis pigmentosa, both rare but potentially blinding diseases.

# **December 2017**: First retinal gene therapy is approved

https://www.youtube.com/watch?v=jTVW-E5Cw2U

# Gene augmentation

## Adeno-associated virus (AAV) vectors for the expression of large transcripts



USH1B

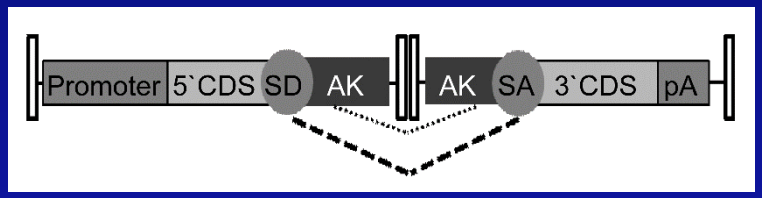
# Gene augmentation

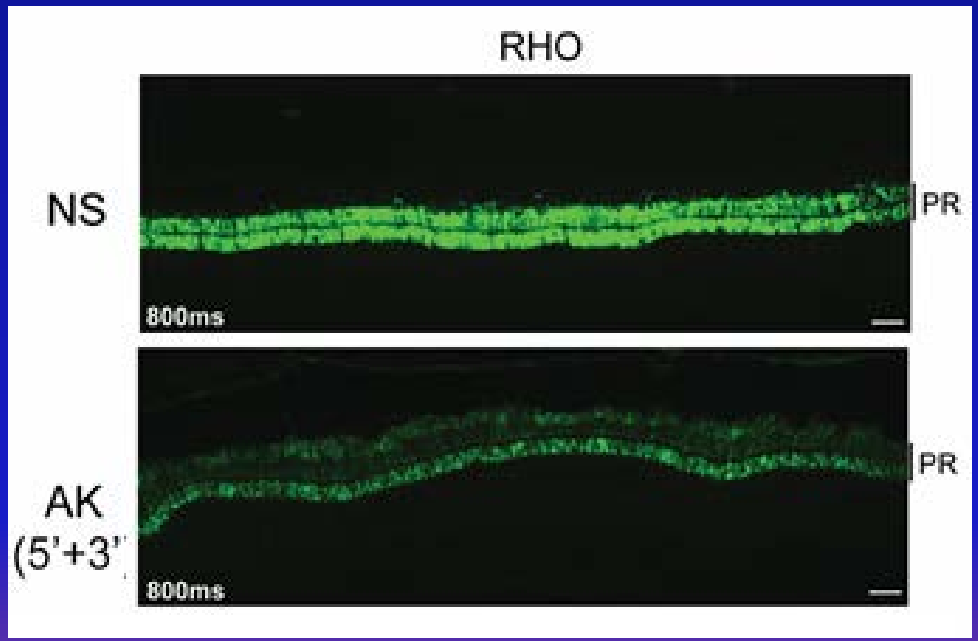
**Alberto Auricchio, Naples, IT**

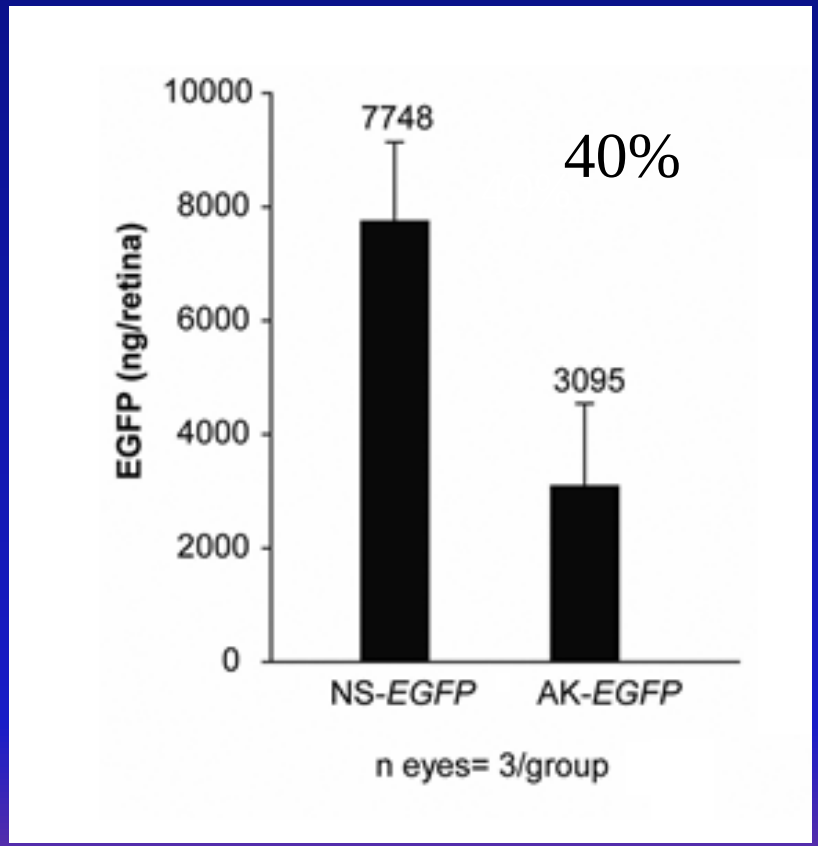
*"Dual AAV vectors for gene therapy of USHIB retinitis pigmentosa"*

## *1- Dual AAV vectors transduce mouse and pig photoreceptors*

Pigs retina

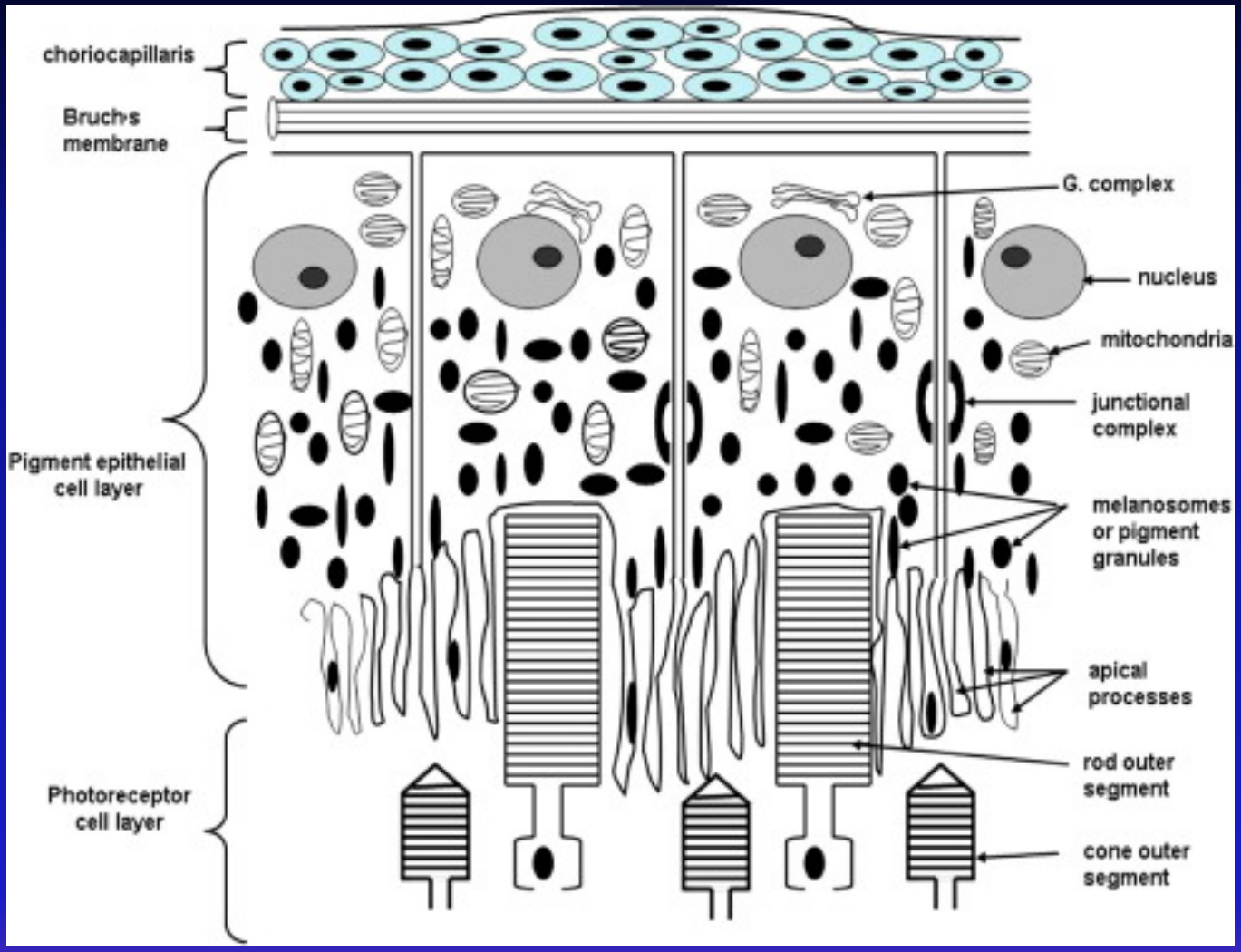



*Colella et al, Gene Therapy (2014) 21, 450–456*

# *2- Dual AAV vectors restore melanosomes and rhodopsin localization in the retina of a mouse model of USH1B*



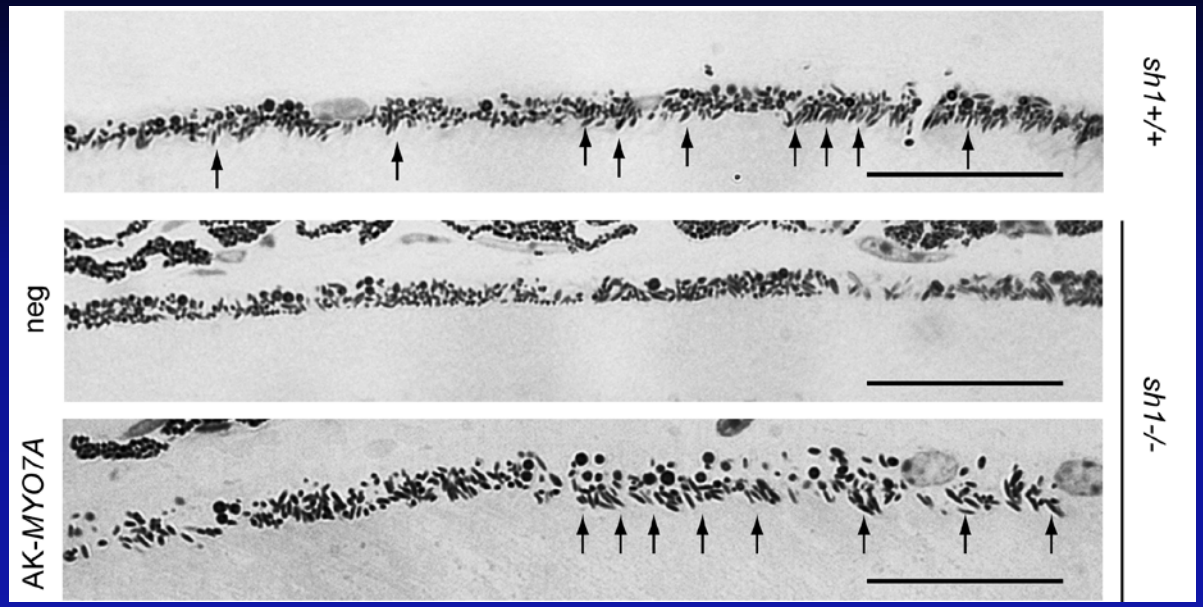

Shaker mice
(Myo7a mutant)

**RPE MELANOSOME MIS-LOCALIZATION**

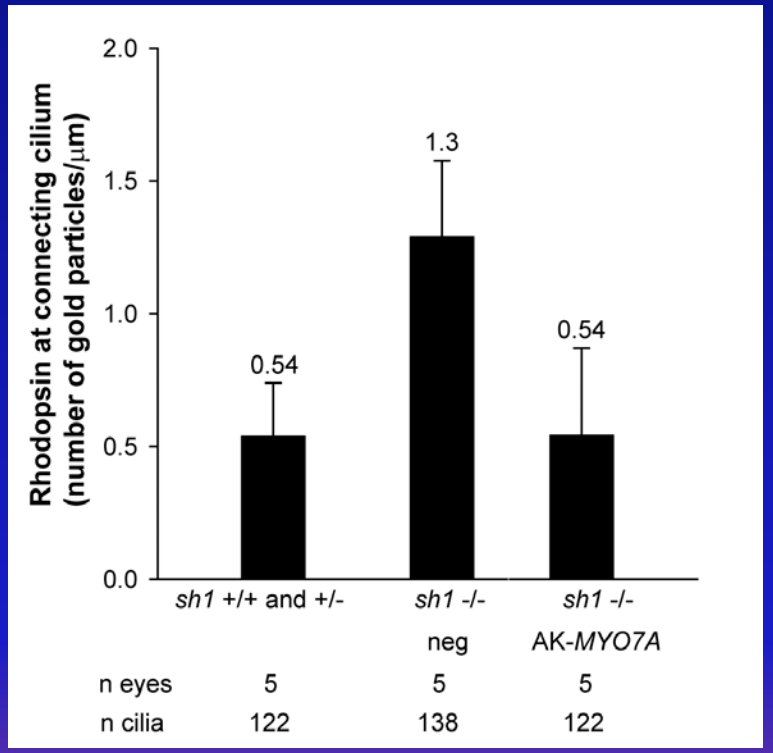
**RHODOPSIN ACCUMULATION AT PHOTORECEPTOR CONNECTING CILIUM**

## *2- Dual AAV vectors restore morphological features in the retina of a mouse model of USH1B*

- Treatment leads to correctly localized melanosomes




- Limits Rhodopsin accumulation at the connecting cilium




*Trapani et al, EMBO Mol Med. 2014 Feb;6(2):194-211*

Horizon 2020

# UshTher

## *Clinical trial of gene therapy with dual AAV vectors for retinitis pigmentosa in patients with Usher syndrome type IB*

**Project ID**: 754848

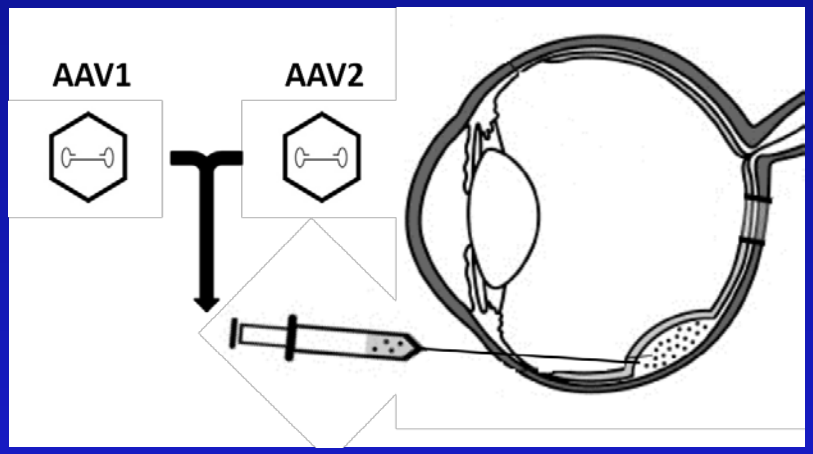
Horizon 2020

Objective:

To test the safety and efficacy of a highly innovative gene therapy approach (dual AAV) in the retina of USHIB patients.

Coordinator:

Fondazion Telethon




Dual AAV8-*MYO7A*

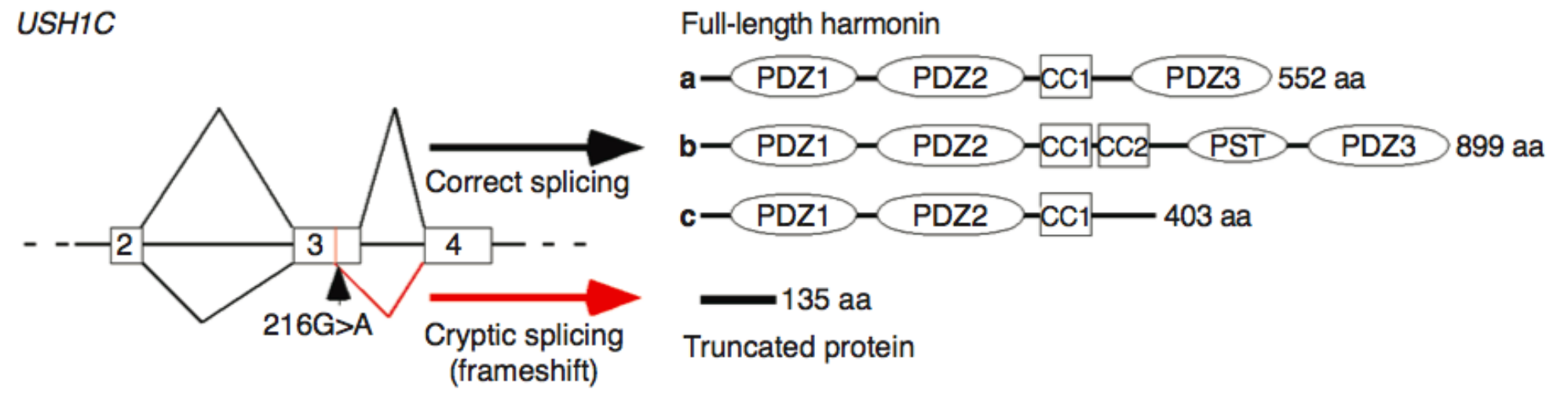
USH1C

# Correction of translation

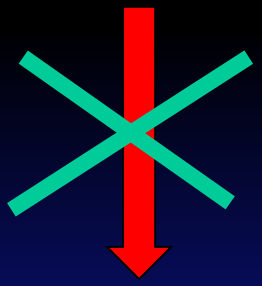

## Jennifer lentz (USH1C)

*"Antisense oligonucleotides effectively treat Usher Syndrome in mice."*

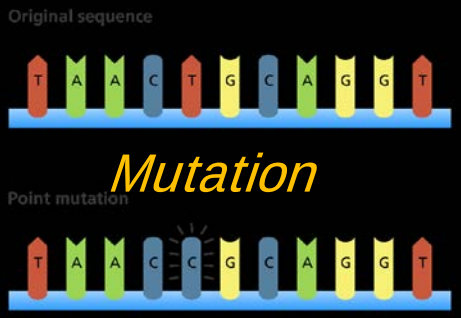
Frame shift mutation found in French-Acadian USH1C patients of Louisiana.
Results in a severely truncated protein and affects all harmonin isoforms



Gene

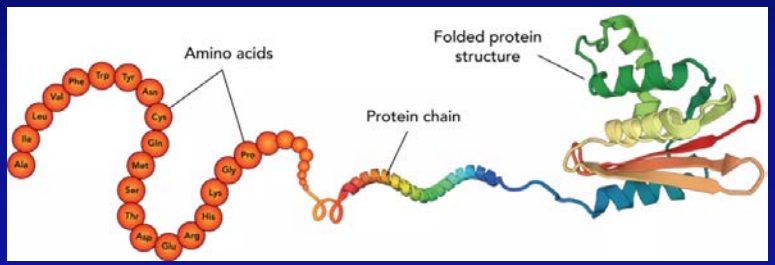


Antisense Oligonucleotide




CRYPTIC SPLICING

Protein




Cell

Organ

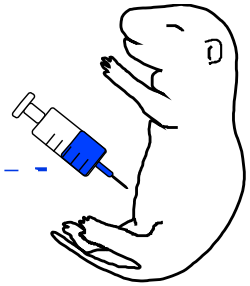
# Delivery of ASOs in Ush1c mice

## Hearing and Balance
Target: Hair Cells

### Systemic

Intraperitoneal Injection (IP)

Sub-cutaneous Injection (SC)

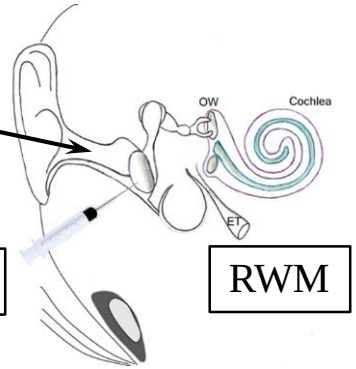


### Local
Tympanic membrane (TM)

Topical-TM

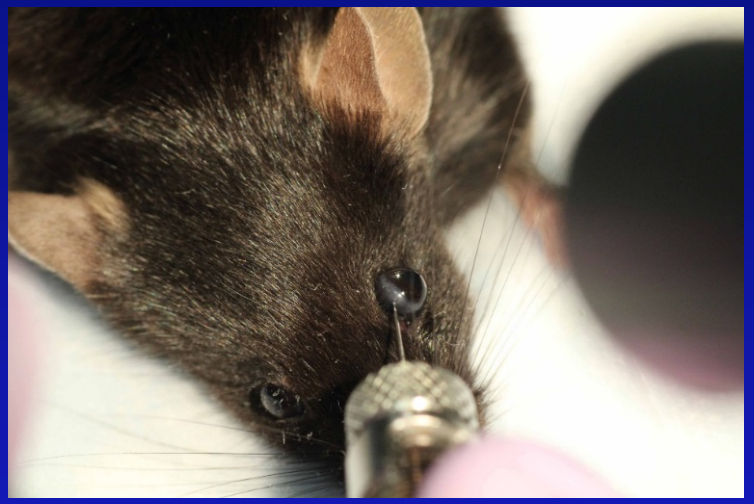
trans-TM

RWM



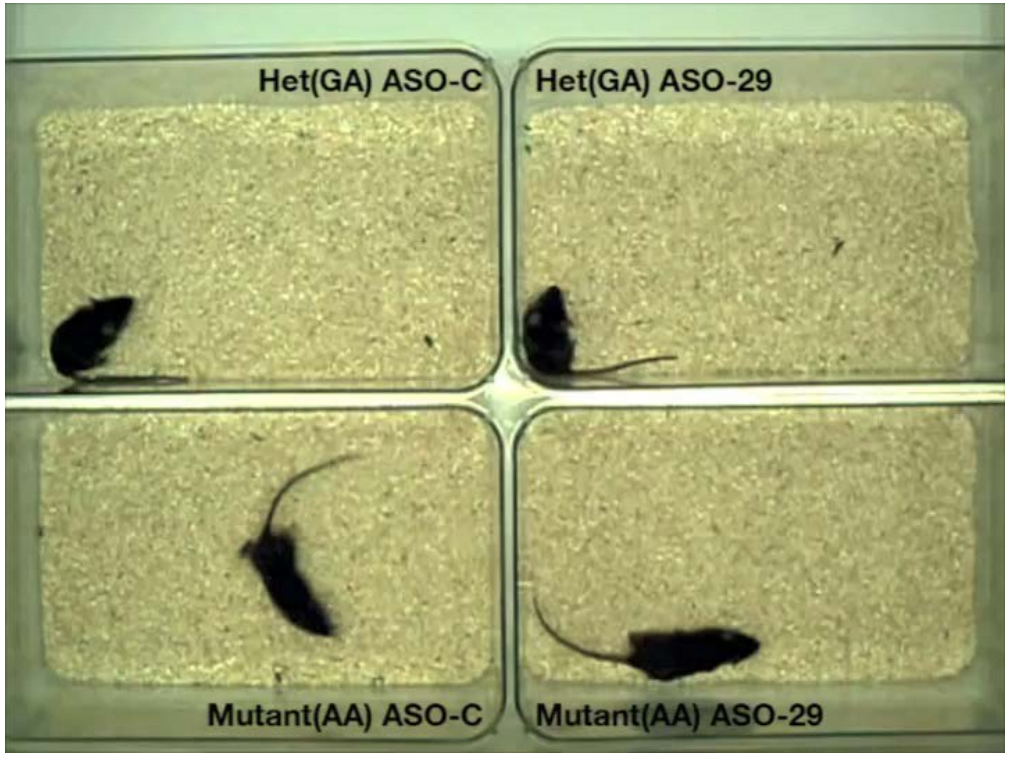

## Vision
Target: Photoreceptors

### Local
Intravitreal Injection (IVI)

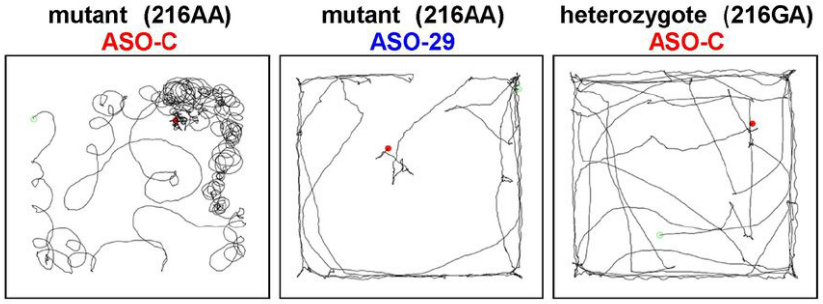


# Systemic and local ASO treatment rescues balance behavior

Open-field Chamber

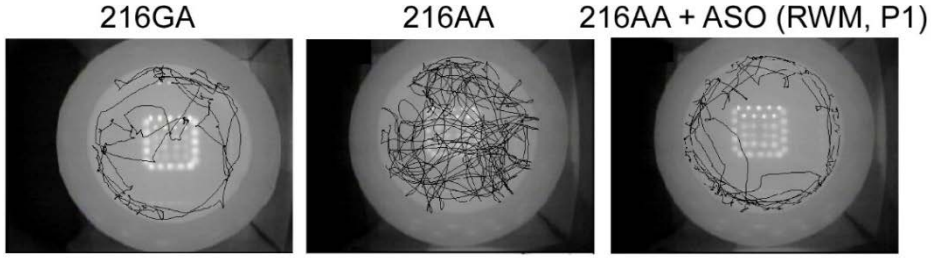



## Systemic Treatment




*Lentz et al 2013*

## Local Treatment



USH2A

# Correction of translation

Erwin van Wijk, Nijmegen, NL

*Antisense oligonucleotides*

Exon skipping: **USH2A e**

mRNA

Function

exon 12 exon 13

++

m

c.2299d

exon 12 exon 13 ex

–

**AON**

exon 12 exon 13 exon 14

+ ?

**In frame** skipping

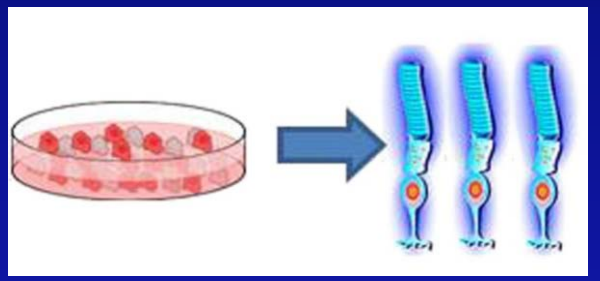
exon 12 exon 14

# Splice-modulation to treat *USH2A*-associated RP

**QR-421a**

AON

&



Zebrafish *ush2a* exon13 knockout:

- Functional rescue!

Patient-derived photoreceptor progenitors

- Specific, non-toxic, effective

**Save vision!**

Preparation of phase1/2 clinical trials: anticipated to commence at end 2018

ProQR™ THERAPEUTICS

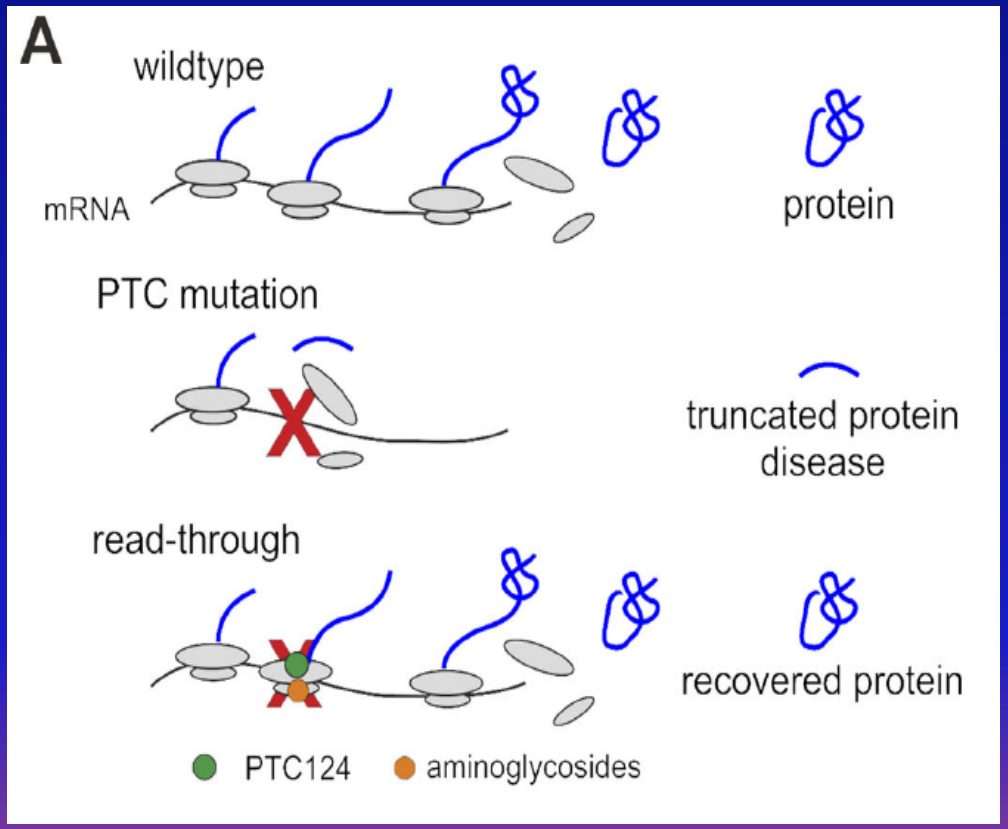
USH1C

# Correction of translation

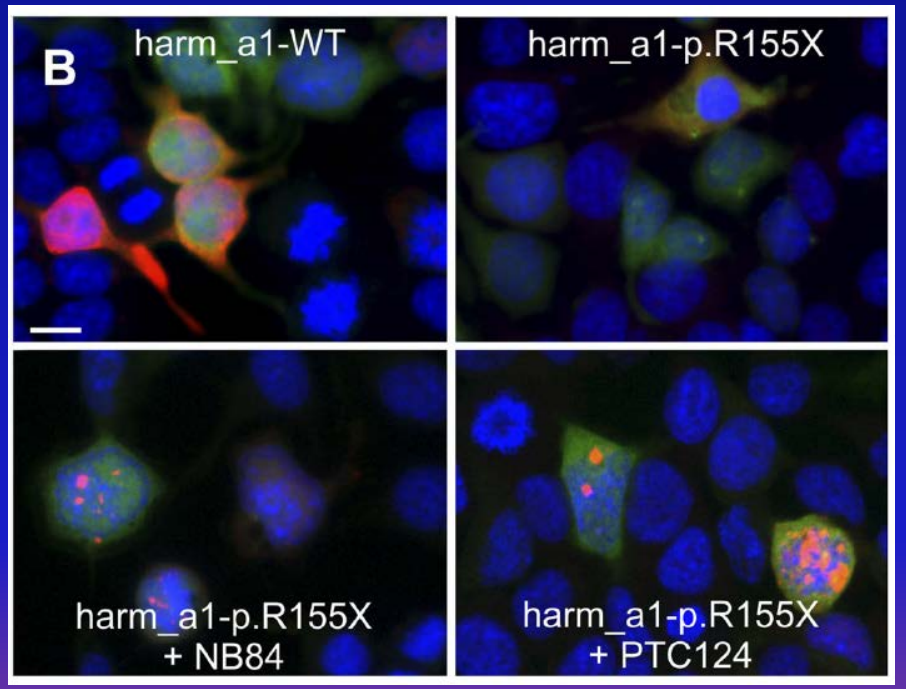
Kirsten Nagel Wolfrum

*"Translation read-through to treat hereditary retinopathy"*

**TRIDS: Drugs that target in-frame non sense mutations (premature stop)-**
**Most studied: Amynoglycosides**




pR155X USH1C in-frame non sense mutation (harmomin: red)



USH2A

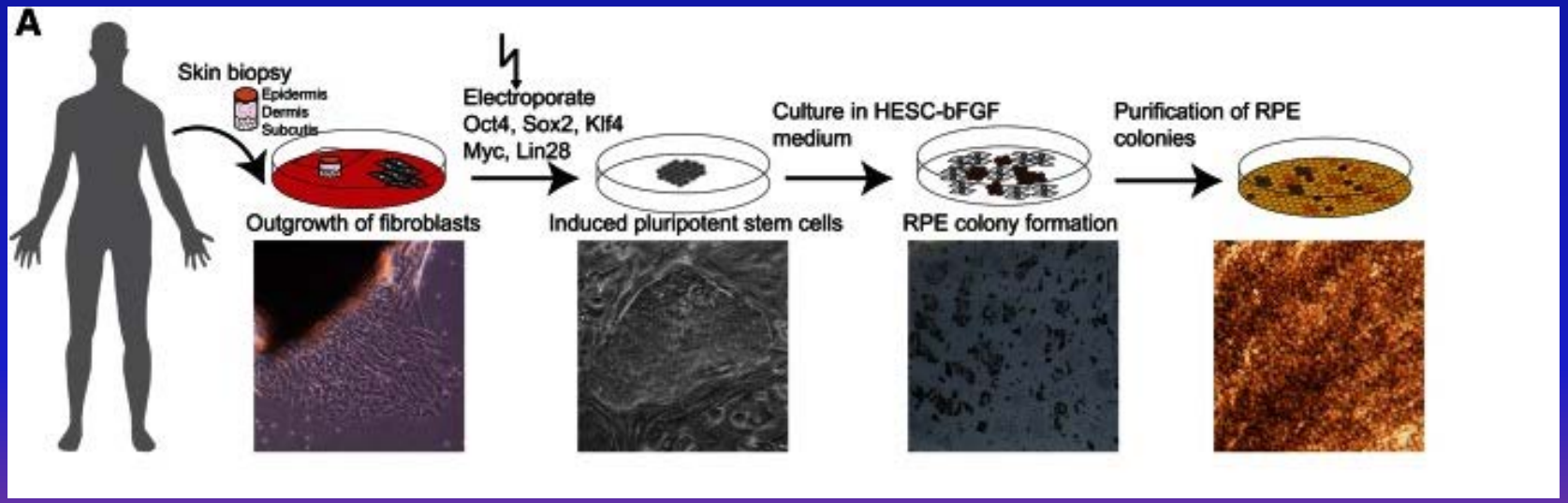
# Correction of translation

Kirsten Nagel Wolfrum

*"Translation read-through to treat hereditary retinopathy"*

**USH2A:** W3955X most common in german population
No expression of Usherin (USH2A protein)
And G3142X mutation

See recovery of expression if treated with TRIDS (Ataluren) at a dose dependent manner. Importantly, we can see expression in patients derived fibroblasts after treatment with Ataluren



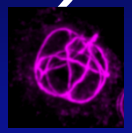

Retinal pigment epithelium cells (RPE) from RP2 R120X patient derived fibroblasts

# Correction of translation

## A pharmacogenetic therapy for targeting nonsense mutations in USH - Ataluren

### Efficacy in transient transfected cells (*USH2A, USH1C)*

Restored protein expression
Functionality

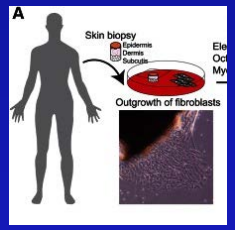


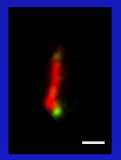
### Biocompatibility

Limited retinal toxicity (mouse; human)
Phase 1 completed

### Efficacy in patient-derived cells

- Protein expression
- Recovered localization
- Recovered ciliary phenotype
- functionality



### Efficacy in animal models

Mice

Pigs
(USH1C_p.R31X)

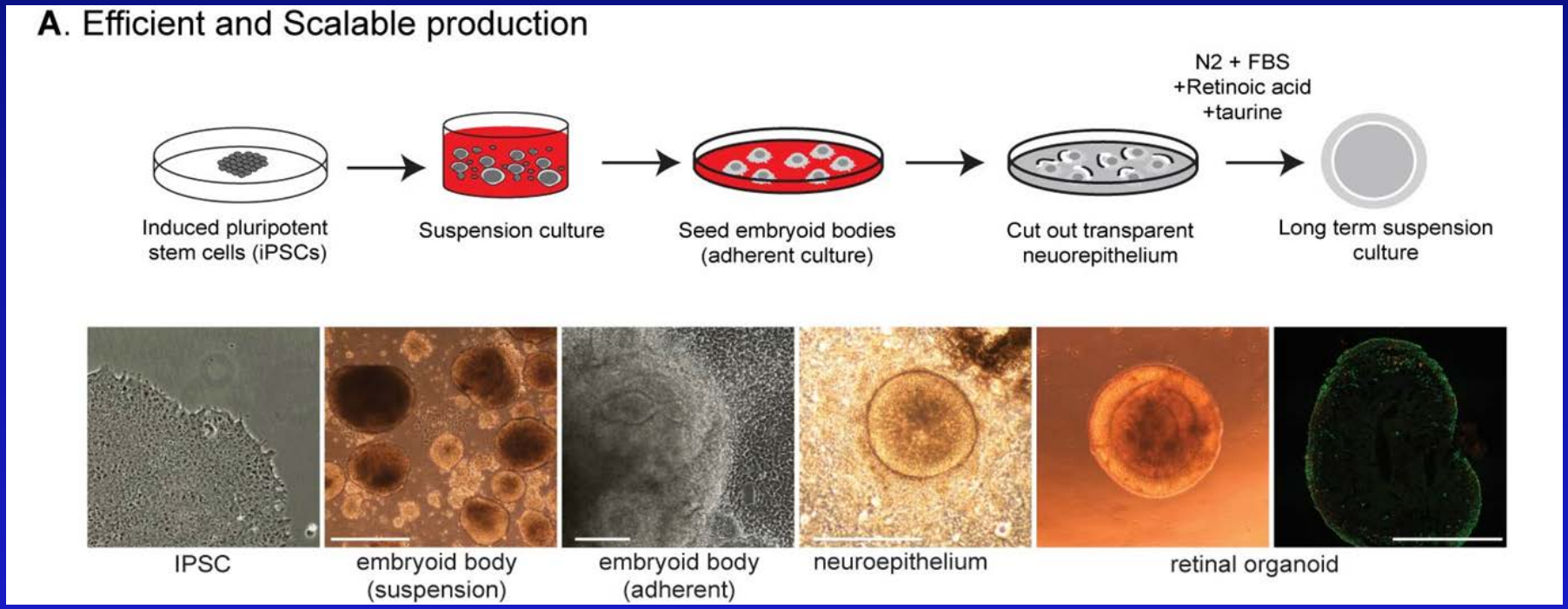
### Clinical trial

Aniridia phase 2 (STAR; NCT02647359)
FUTURE: Usher syndrome?

JOHANNES GUTENBERG UNIVERSITÄT MAINZ

# Retinal organoids as disease model

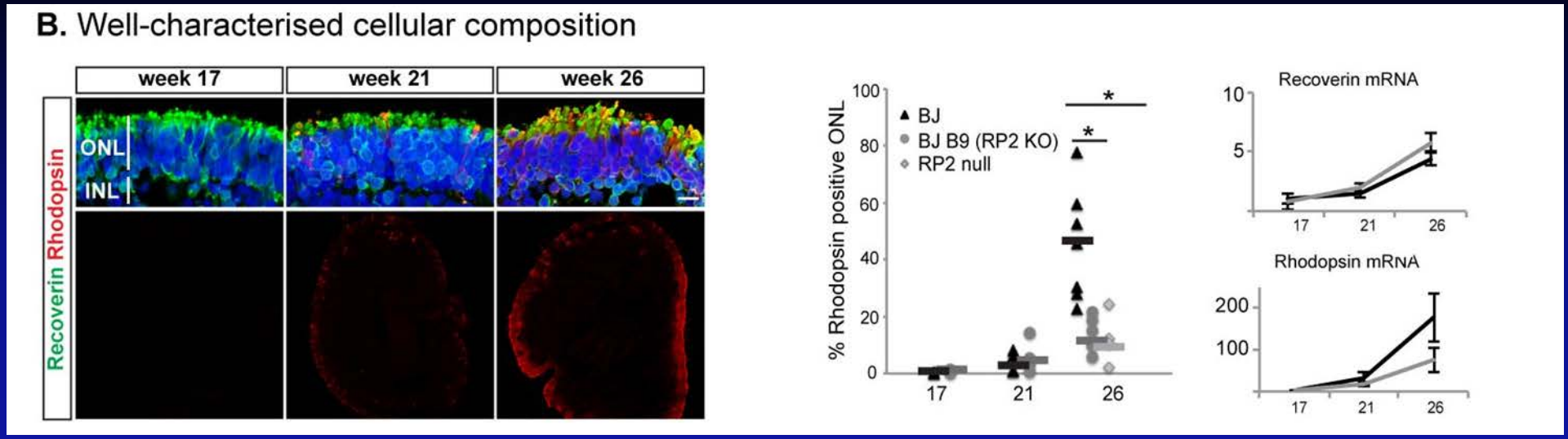
Mike Cheetham (UCL, London)

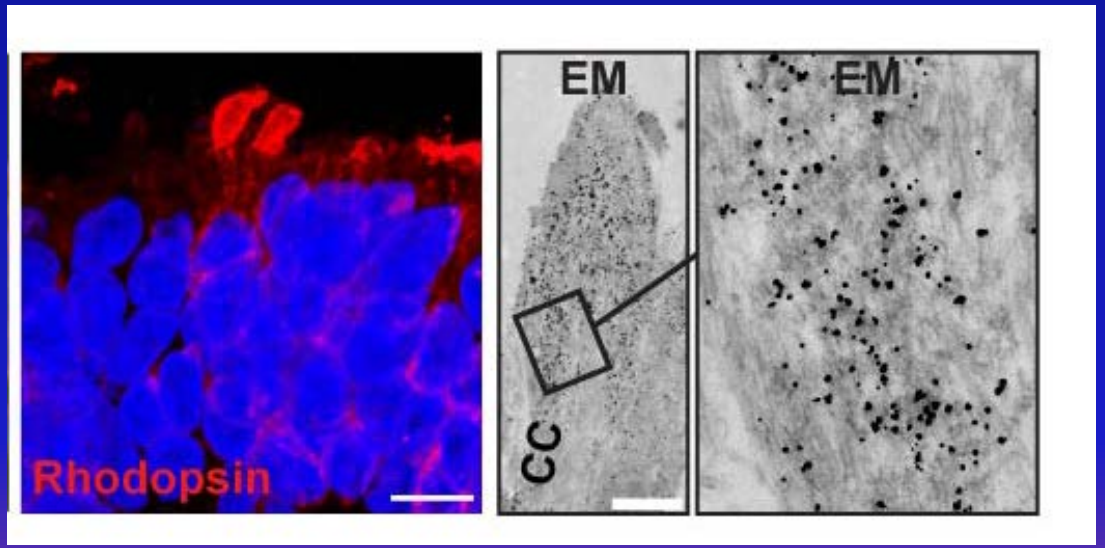



*Parfitt, Lane, Ramsden et al Cell Stem Cell 2016*
*Burgoyne et al PLoS One 2018*

# Retinal organoids as disease model

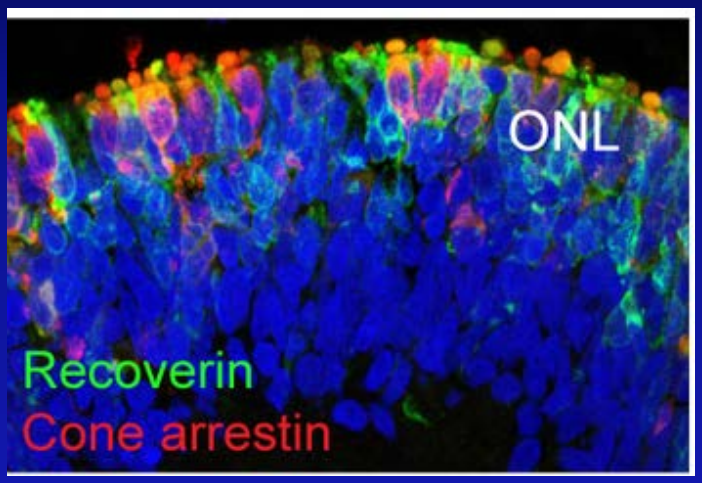
## Mike Cheetham (UCL, London)

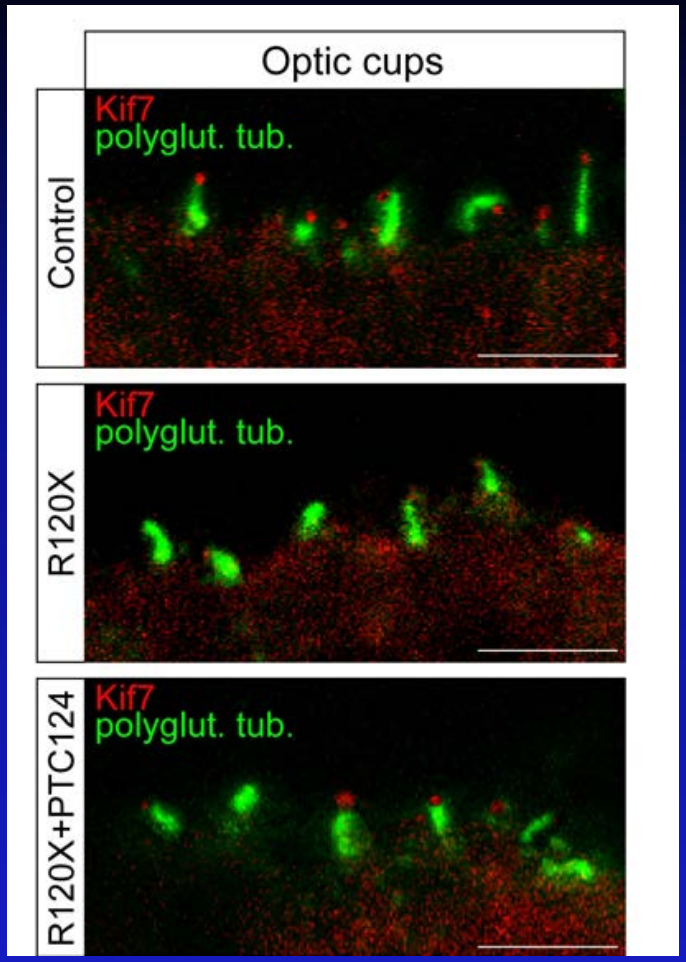


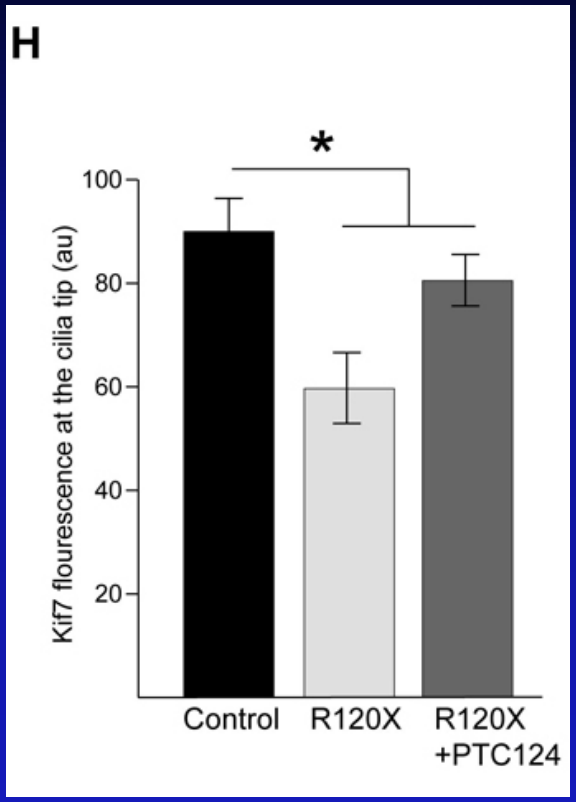



# Retinal organoids as disease model

±PTC124



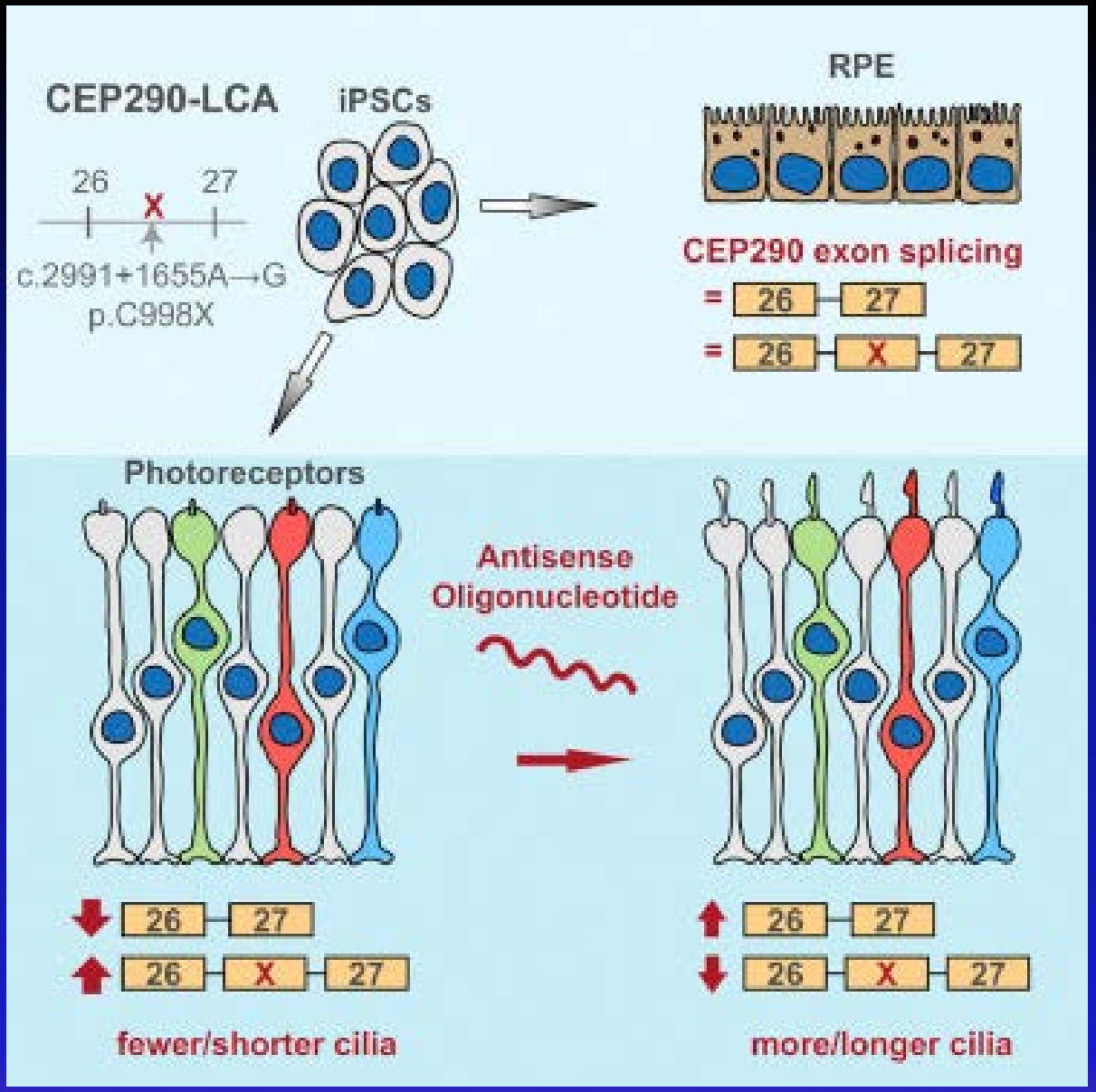




PTC124 partially restores RP2 function in retinal organoids and is a good candidate for a clinical trial for RP2 stop mutations

*Schwarz et al. 2017 – Hum Mol Genet.* 26 (13): 2480-2492

# Retinal organoids as disease model




*Parfitt, Lane, Ramsden et al Cell Stem Cell 2016*

*Dulla, Aguila et al Mol Therapy Nucleic Acids in press*

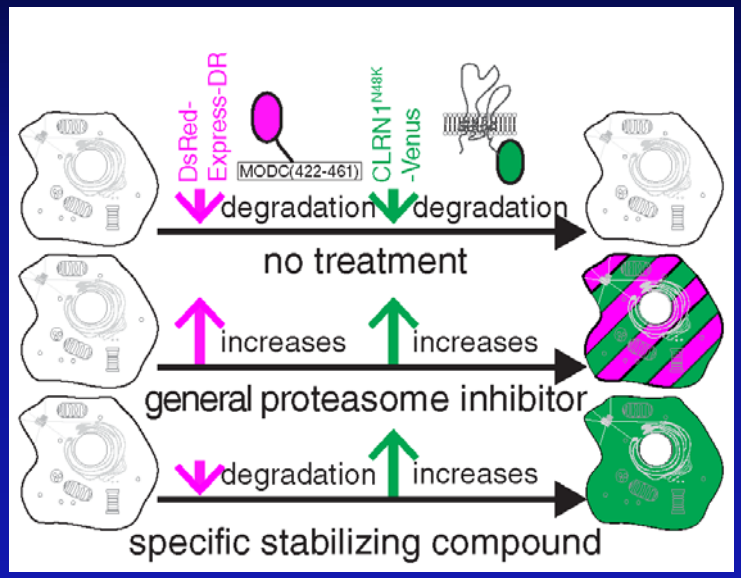
USH3

# Small molecules and pharmacology

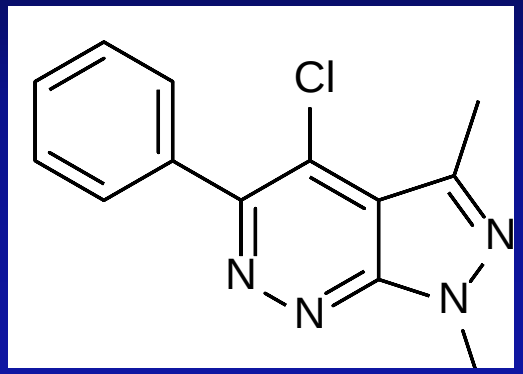
Yoshikazu Imanishi

***"A small molecule mitigates hearing loss in a mouse model of Usher syndrome III."***

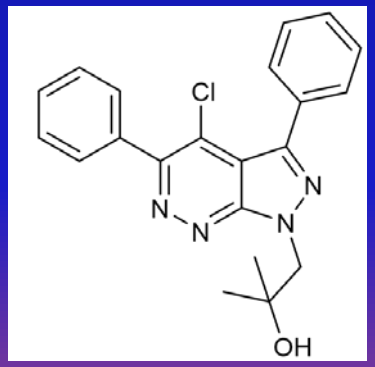
Novel method for screening molecules




New molecule




Improved molecule




Proof of Concept!

Provided by Yoshikazu Imanishi

# THE FUTURE IS IN OUR POWER!

# The many faces of Usher Syndrome Research