USH Talks

Therapies to preserve vision in Usher syndrome

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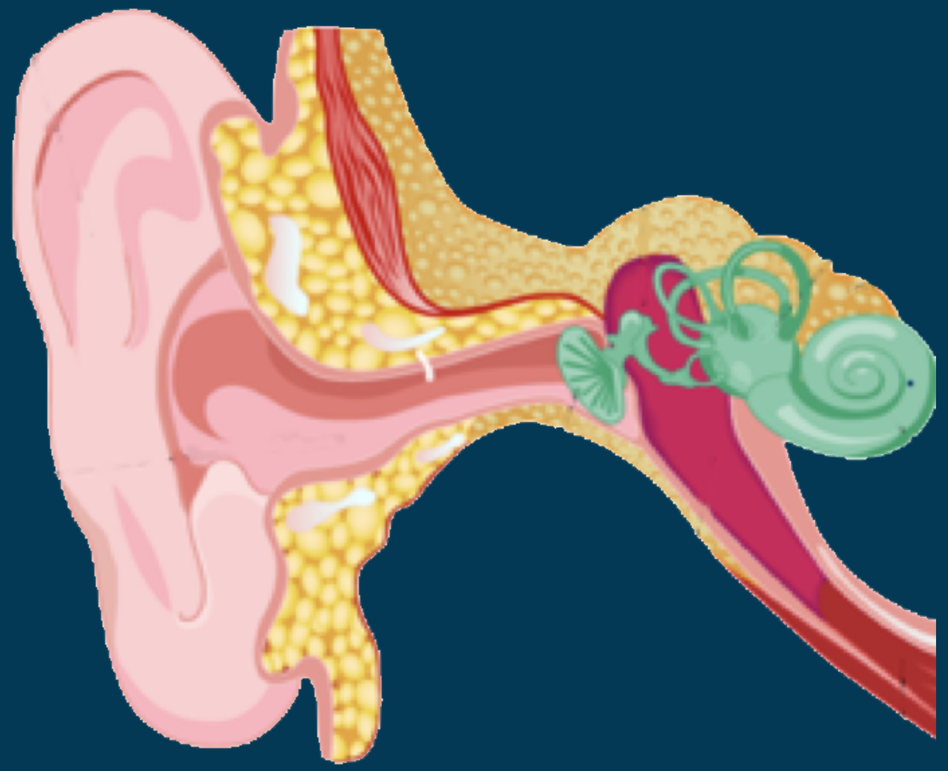
- Gene therapies are being developed
- For gene therapies to work, we need to save cells from dying
- Therapies that protect cells from dying may enhance the efficacy of gene therapies

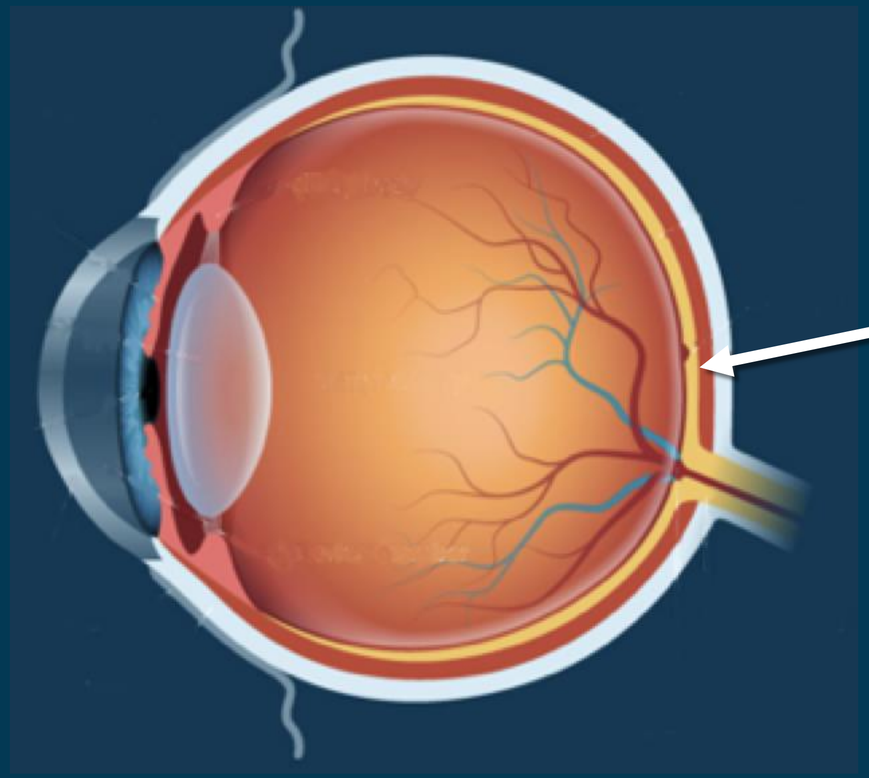
Mechanosensory cells in the inner ear detect sound



Mechanosensory cell
in the inner ear

http://www.aurismedical.com

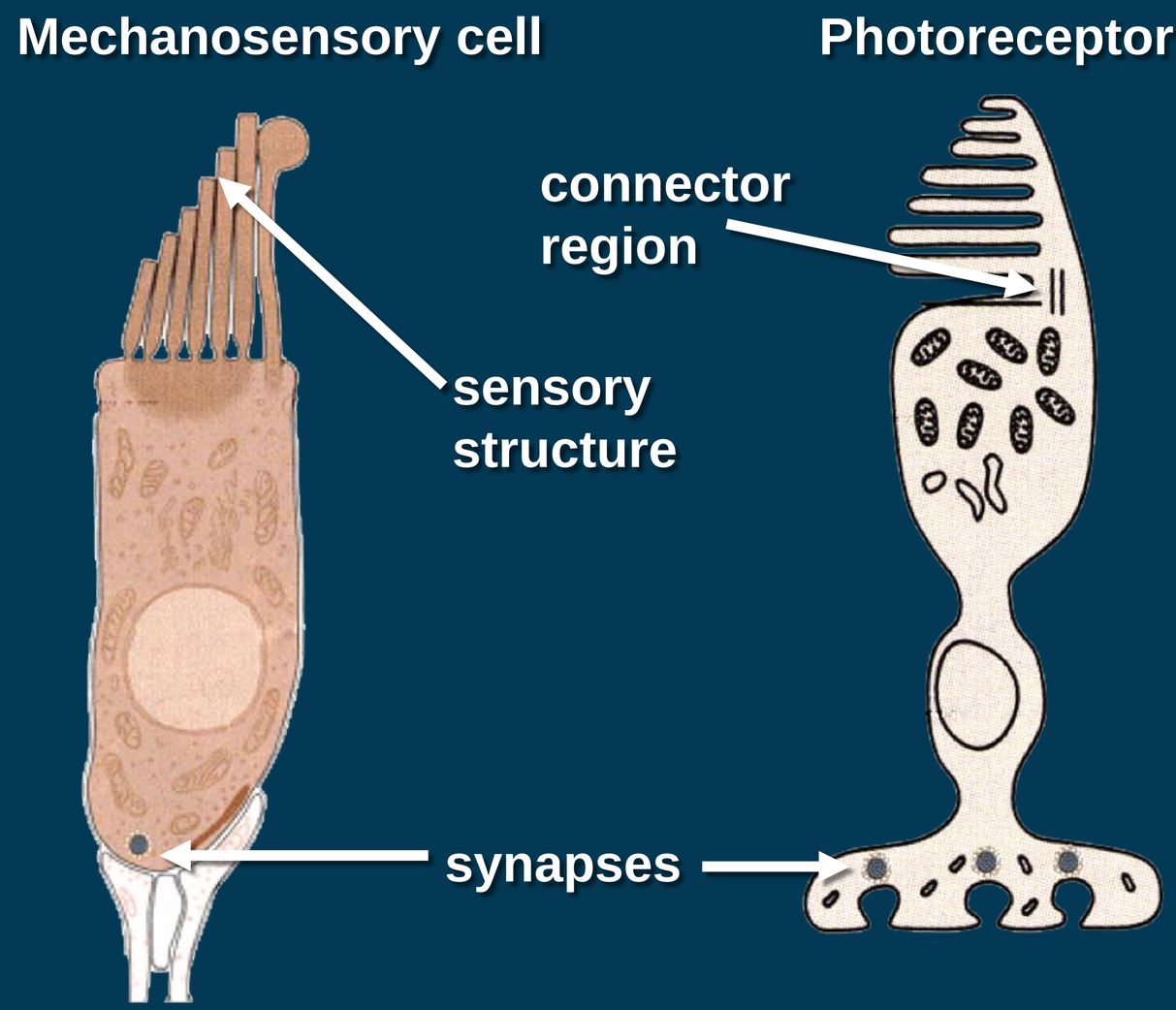
Photoreceptor cells in the eye detect light



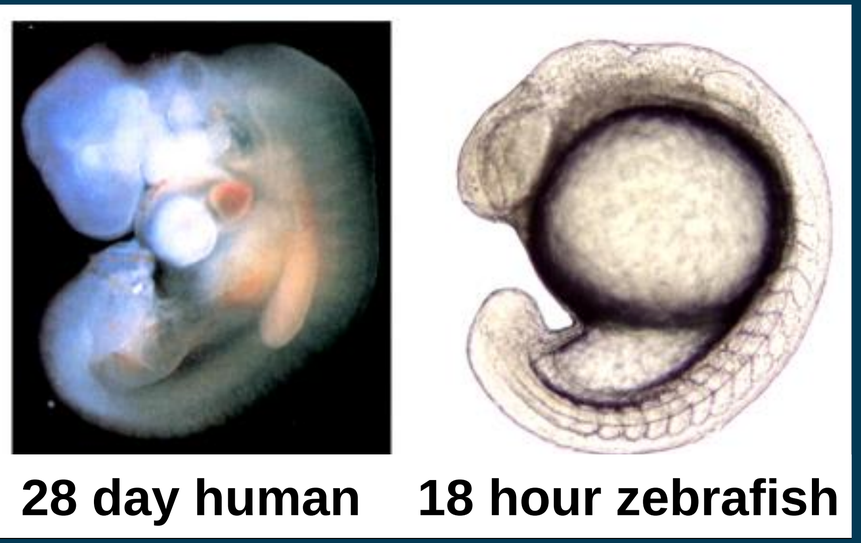
Photoreceptor
in the retina

(http://www.allaboutvision.com)

Usher proteins function in mechanosensory cells and photoreceptors

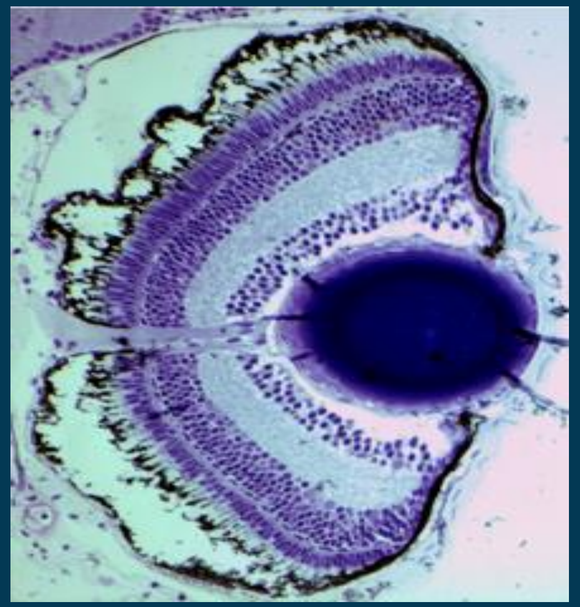


Zebrafish provide excellent models for studying Usher syndrome



28 day human

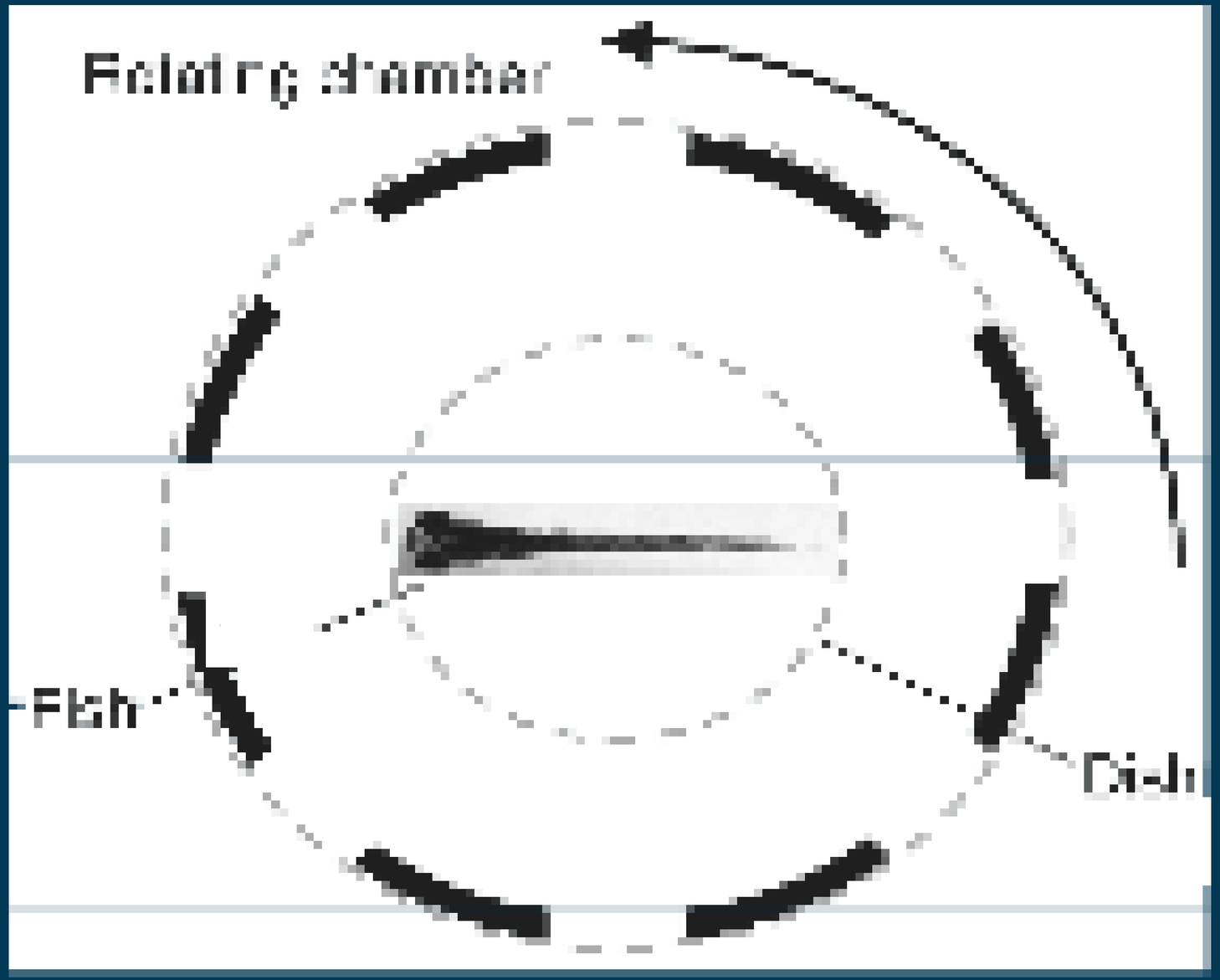
18 hour zebrafish



Zebrafish:

- retinal and inner ear cells are similar to humans
- have the same USH genes
- USH gene mutations produce retinal and inner ear cell death
- have advantages for drug screening

Measuring vision in young zebrafish



Measuring vision in young zebrafish

Normal

Mutant

(Maldonado et al., 2006)

Balance defects in *USH1B* mutants

(Teresa Nicolson)

Acoustic startle response

(Teresa Nicolson)

Lack of response in *USH1B* mutants

(Teresa Nicolson)

How do USH gene mutations result in cell death?

We know that:

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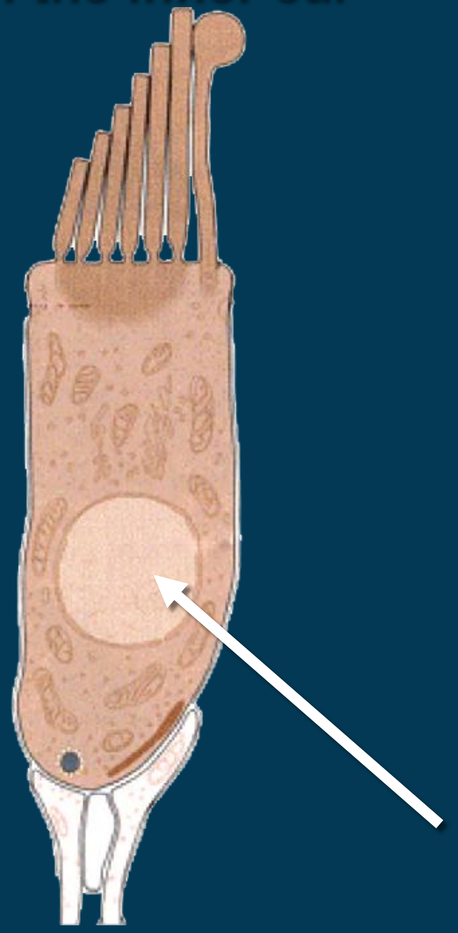
So in USH, when and where in the cells is there a problem with these proteins, and how does this lead to cell death?

Steps in the production of proteins

Mechanosensory cell
in the inner ear



DNA in nucleus
produces RNA

Steps in the production of proteins

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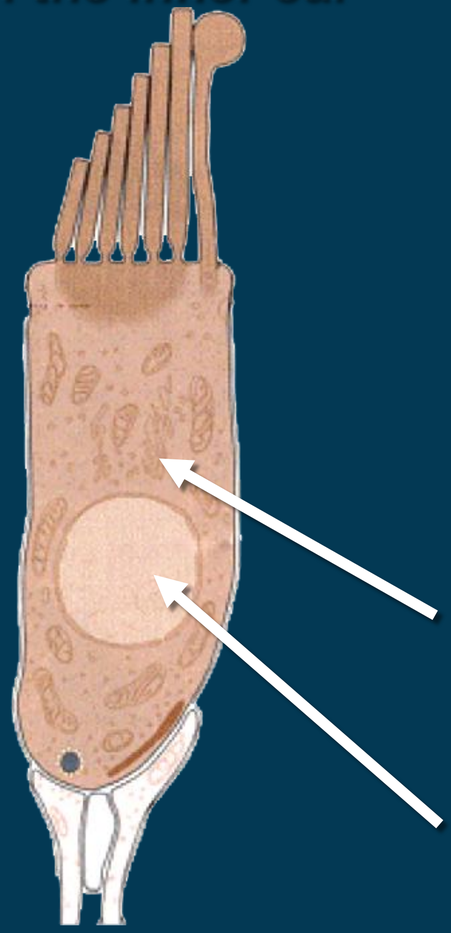

RNA travels to ER

DNA in nucleus
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Steps in the production of proteins

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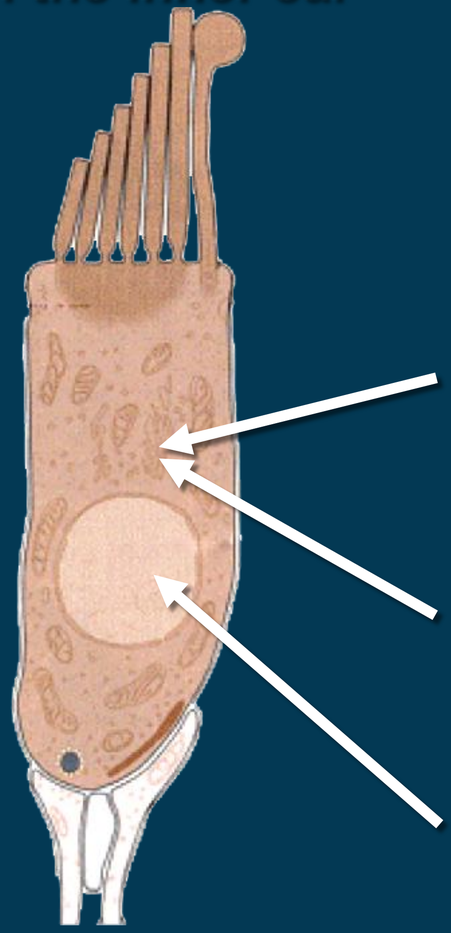

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Steps in the production of proteins

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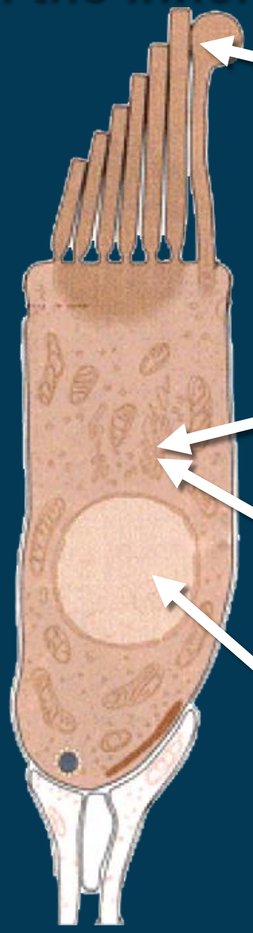
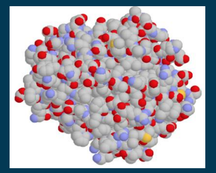


Protein is transported
to functional site



ER translates RNA
to protein

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DNA in nucleus
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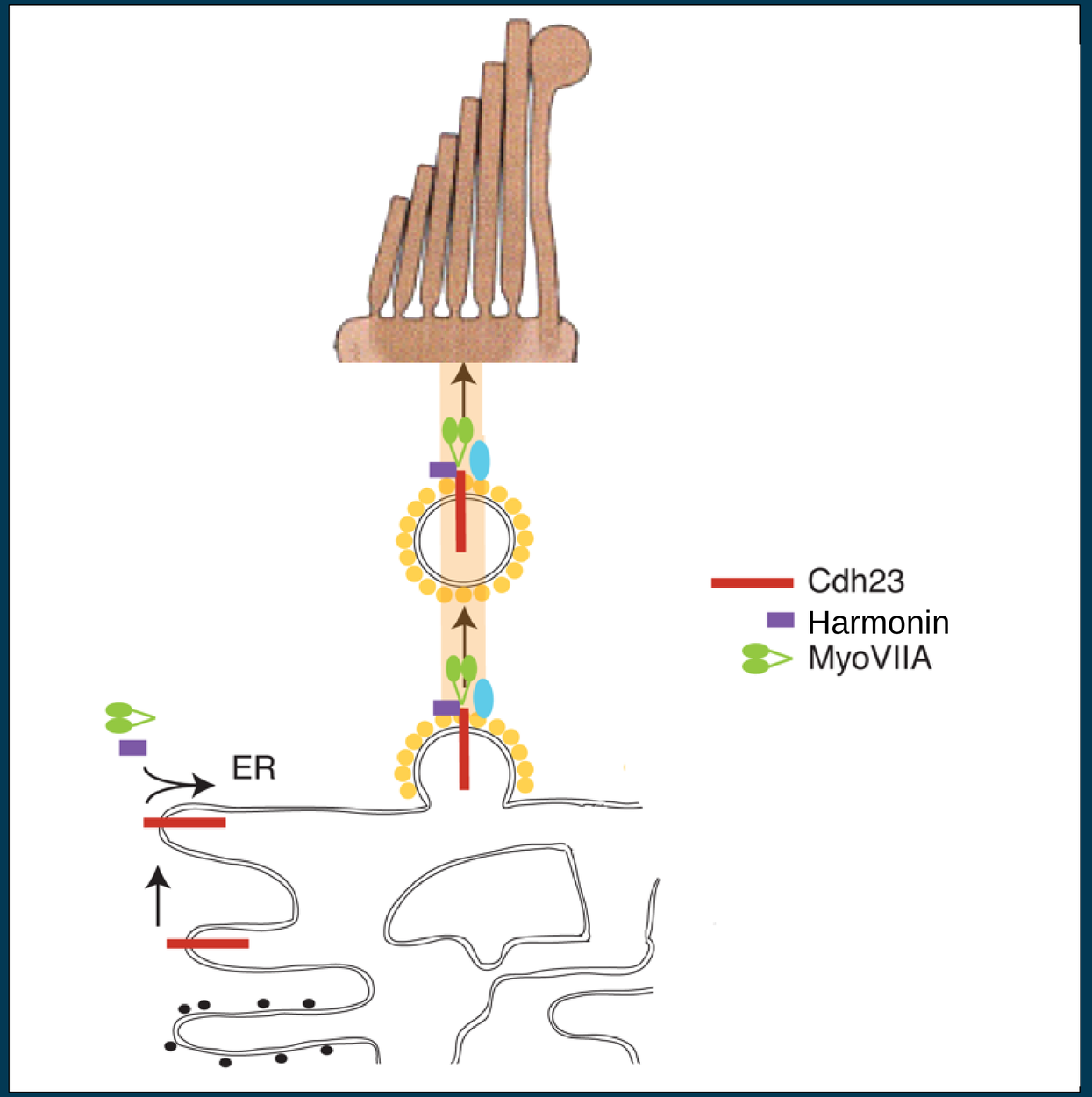
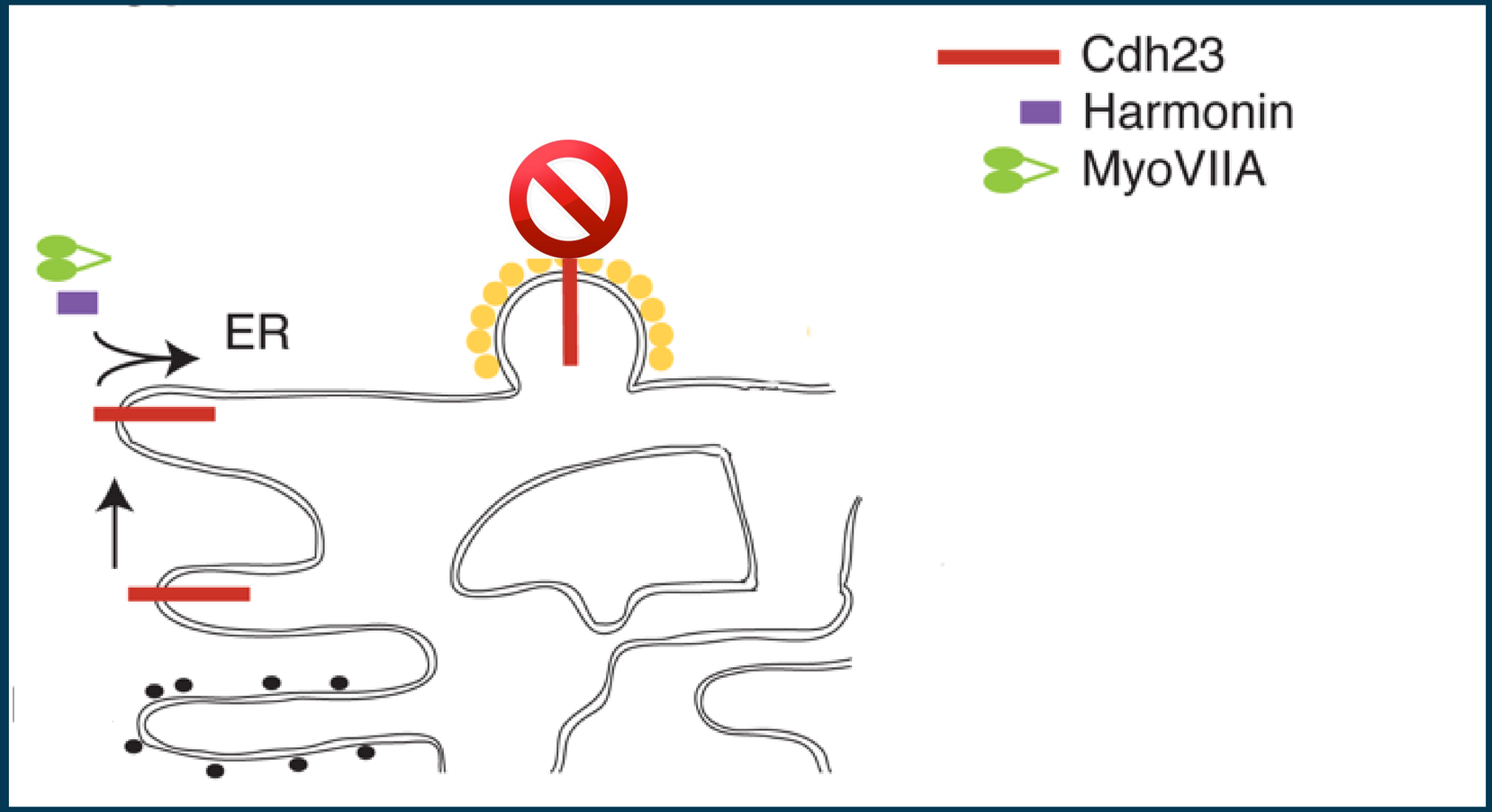
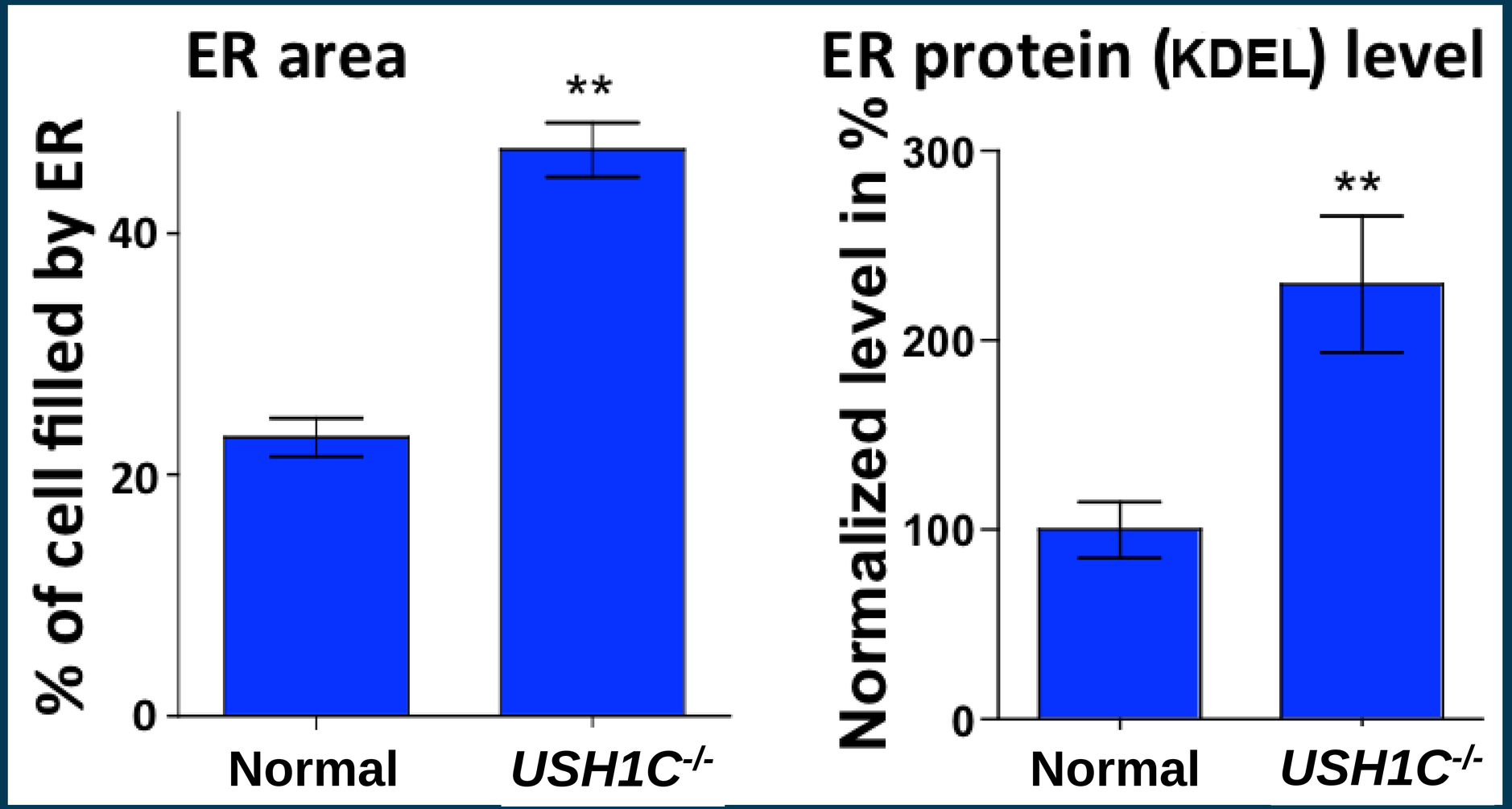
Usher protein complexes form at the ER



Usher mutations block complex formation and Usher proteins accumulate in the ER

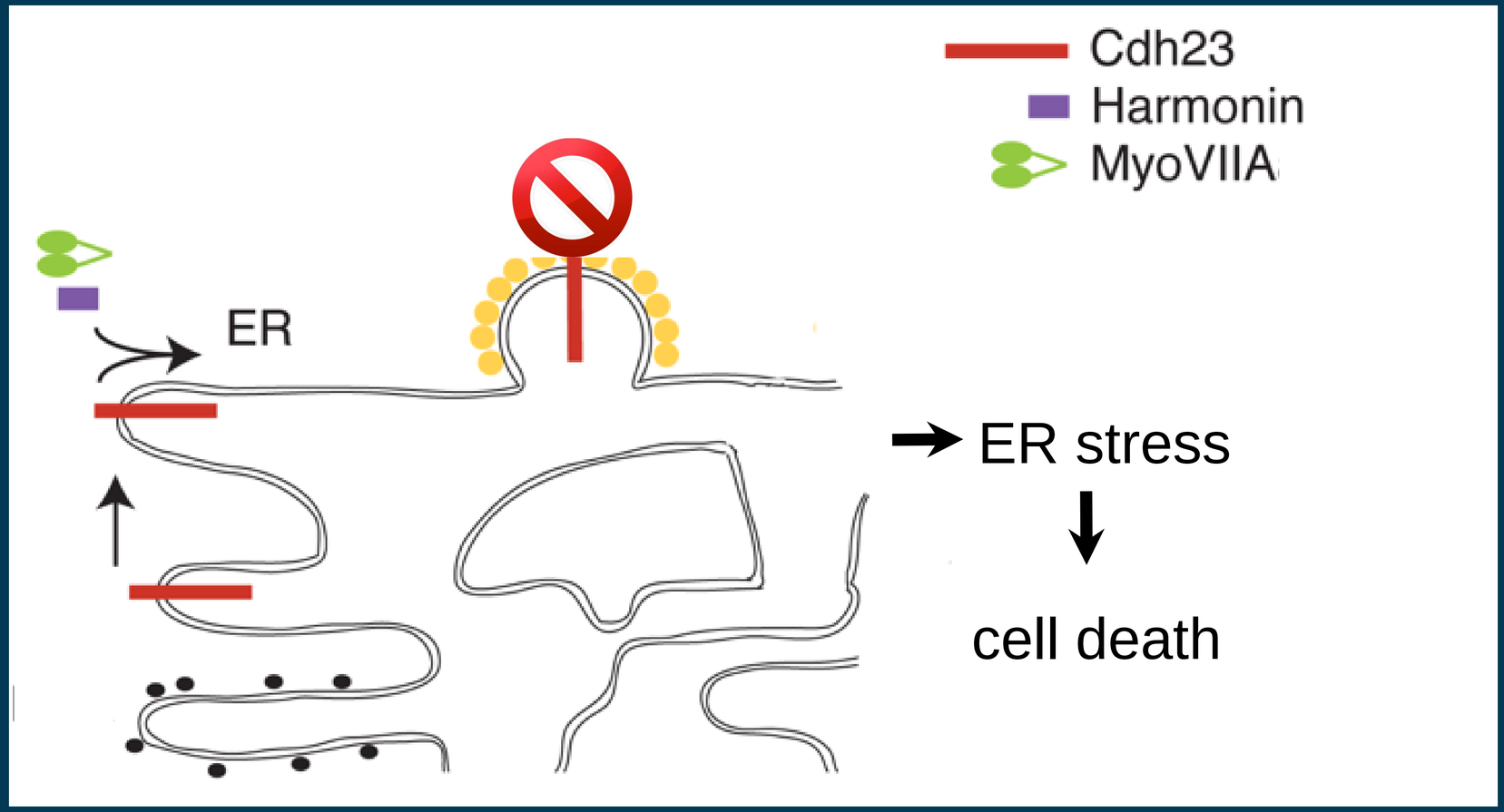


Usher mutations induce ER stress

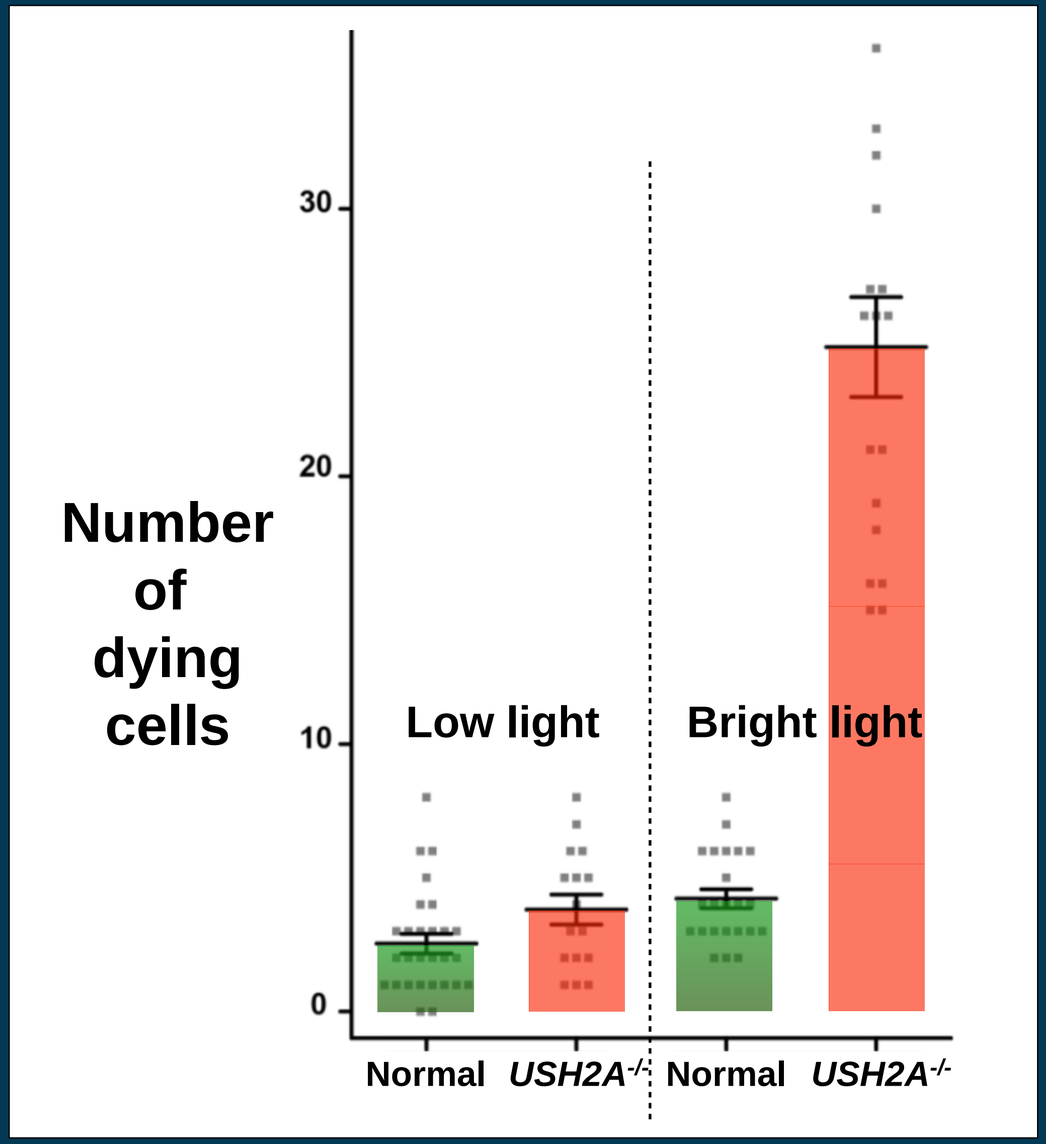


(Blanco-Sánchez et al., 2014)

Usher mutations lead to ER stress and cell death



Exposure to bright light increases the rate of retinal cell death in *USH2A* mutants



(Jennifer Phillips & Kimberly Lerner)

Summary

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- Approved drugs and drugs in development reduce ER stress in Alzheimer's, Parkinson's, and other neurodegenerative diseases
- We use zebrafish models of USH to test these and other potential therapies
- Sun glasses are probably important for USH patients to protect the retina

(https://drawception.com/game/MmqCMTH4Be/undyne-from-undertale)

Therapies to preserve vision in Usher syndrome

University of Oregon

- Bernardo Blanco-Sánchez
- Aurélie Clément
- Taylor Howat
- Judy Peirce
- Jennifer Phillips
- Jeremy Wegner
- Monte Westerfield

Radboud University Medical Center

- Margo Dona
- Erwin van Wyjk

Sponsored by the the Usher 1F Collaborative,
the National Institute of Child Health & Development,
the National Institute on Deafness & Other Communication Disorders,
the National Eye Institute, and the Megan and Vision for a Cure Foundations

VisionForACure.com