

# USHER III INITIATIVE

Developing a drug therapy for both vision  
and hearing loss in individuals diagnosed  
with Usher III

# Discovery of Usher Syndrome

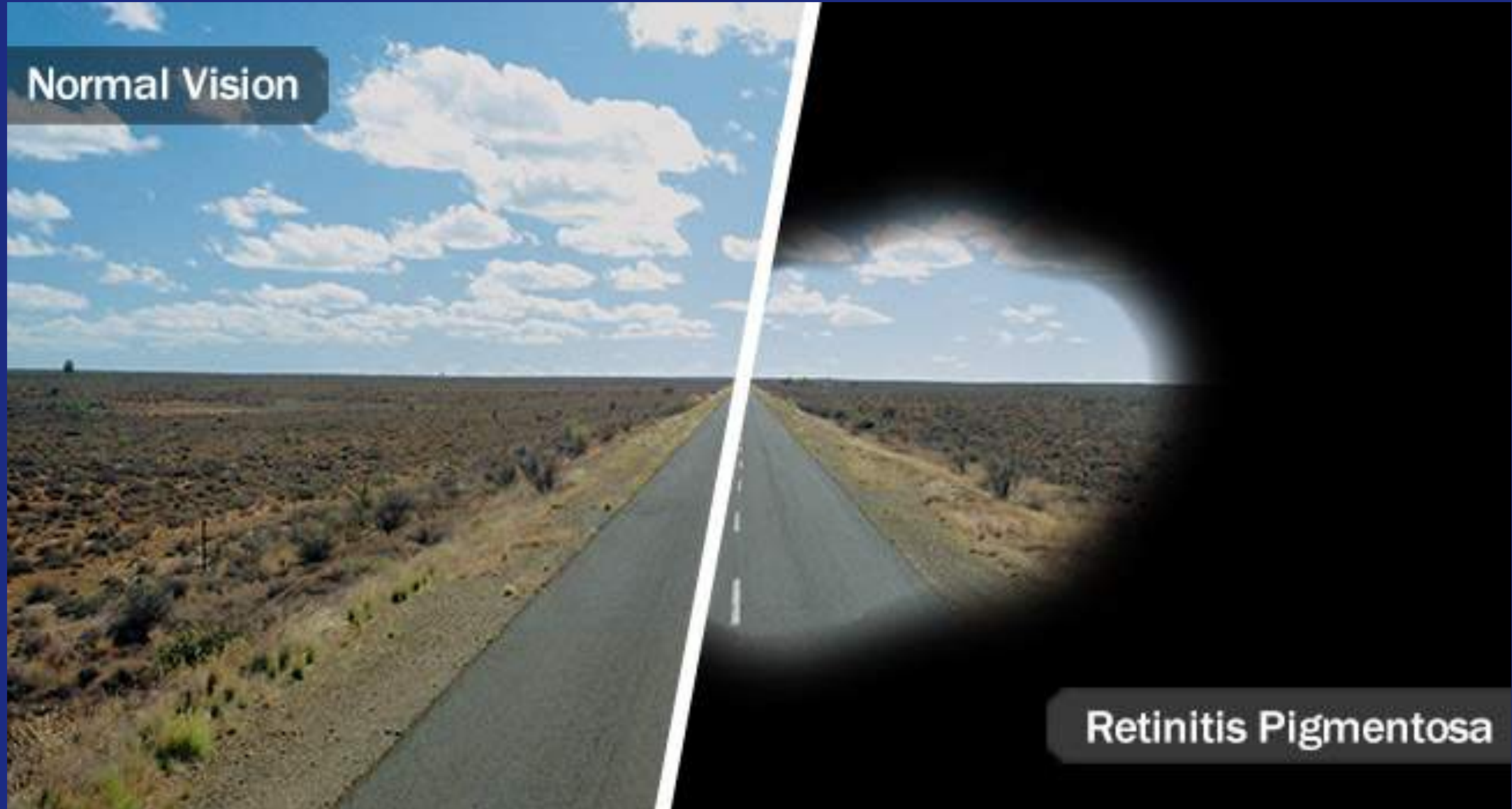
Named for Charles Usher, whose 1914 study of the pathology and transmission of the disease identified its hereditary nature



# Finger Test to Assess Peripheral Vision



# Tunnel Vision



Normal Vision

Retinitis Pigmentosa

# A Pioneer in Inherited Retinal Diseases



Dr. Eliot Berson

- Discovered that ERGs can detect defects in photoreceptors up to 10 years prior to onset of RP
- Discovered first genetic defects associated with RP
- Professor of Ophthalmology at Harvard Medical School (1968-2017)
- Founding Director of the Berman-Gund Laboratory for the Study of Retinal Degenerations at Mass. Eye and Ear

	Type 1	Type 2	Type 3
Hearing	Profound hearing loss or deafness at birth.	Moderate to severe hearing loss at birth.	Progressive hearing loss in childhood or early teens.
Vision	Decreased night vision by age 10, progressing to severe vision loss by midlife.	Decreased night vision by adolescence, progressing to severe vision loss by midlife.	Varies in severity and age of onset; night vision problems often begin in teens and progress to severe vision loss by midlife.
Balance (vestibular function)	Balance problems from birth.	Normal balance.	Normal to near-normal balance in childhood; chance of later problems.

There are many variations in the clinical symptoms of Usher syndrome, therefore the classification of Usher types 1, 2, and 3 must be supported by genetic testing



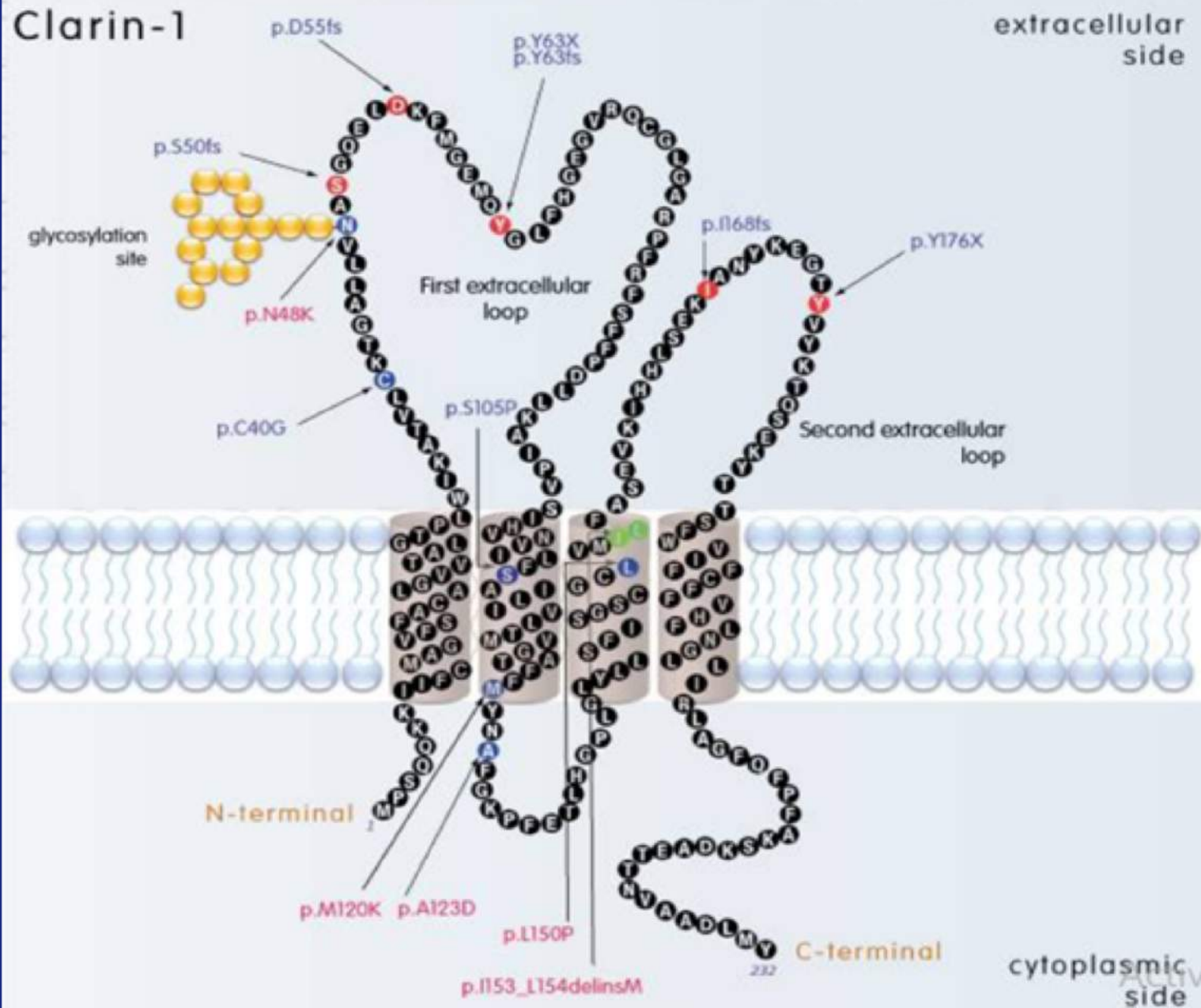
Richard and Cindy Elden

# *Clarin-1 (CLRIN1)*

- Research shows that the same pathology is likely responsible for the auditory and visual loss associated with USH3: defects in the CLRIN1 gene, which encodes the CLRIN1 protein
- *CLRIN1* protein is found in the retina and hair cells in the inner ear, and likely plays a critical role in maintaining the structure of these sensory cells
- There are 15 known pathogenic mutations in *CLRIN1*. The two most common are: p.Y176X and p.N48K



# Clarín-1

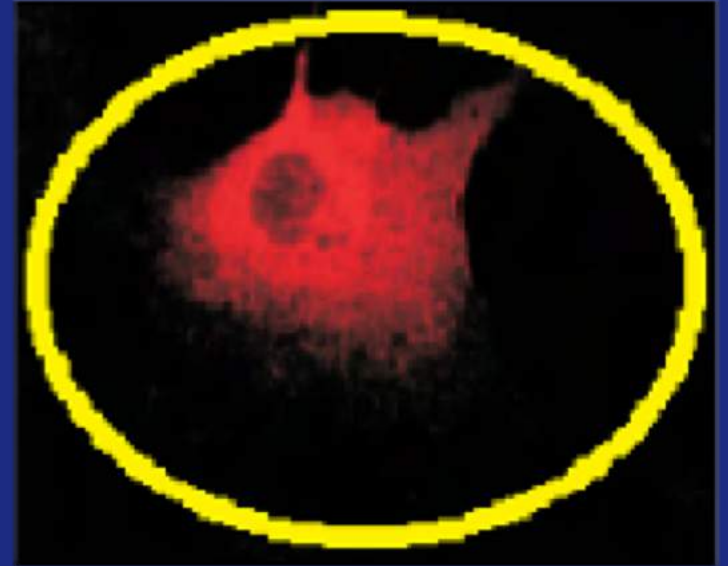


*Clarín-1* Protein Structure Showing Amino Acid Chain and Glycosylation Site

# Localization of *Clarin-1* Protein



Normal protein (red) covers the cell surface bound to the plasma membrane



Mutated protein (red) only present inside the cell (yellow)

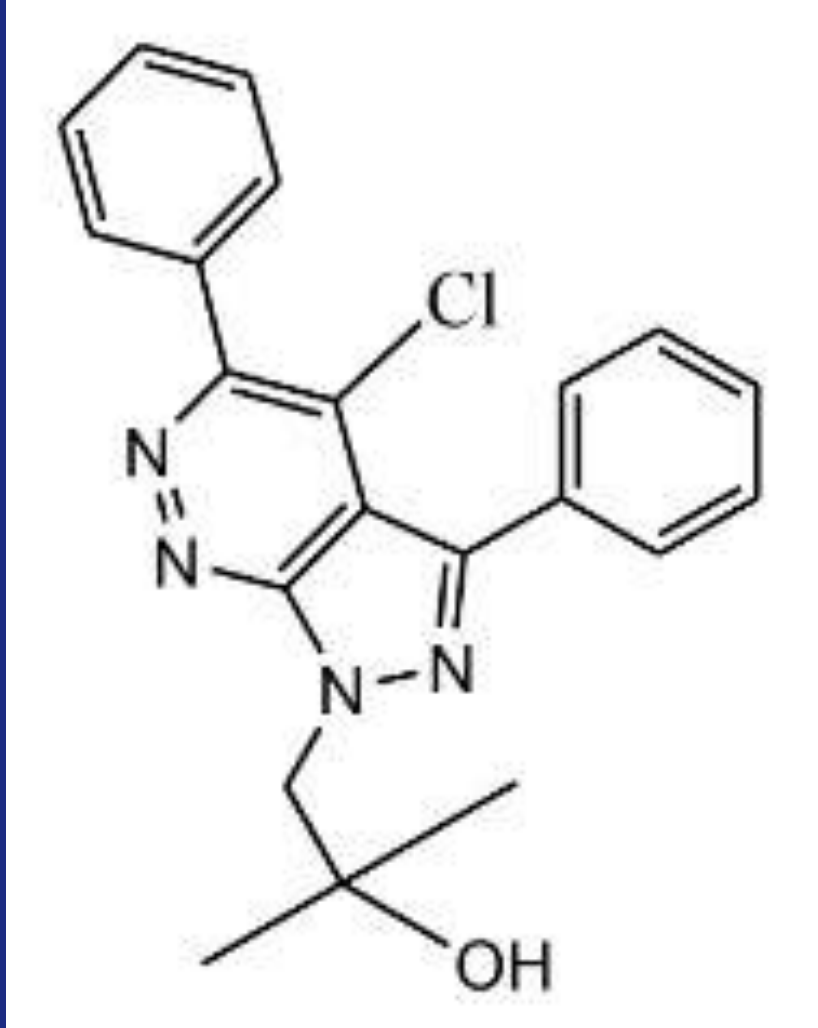
# Gene Therapy

- Relatively new technology; still being refined
- Injecting a viral vector into the nucleus of the cell and modifying the mutated *clarin-1* gene in the inner ear successfully preserved hair cells in the cochlea in USH3 mouse models
- Few clinics have the capability to inject into the ear and the eye directly, and this procedure can be uncomfortable for patients and lead to serious problems, like infection
- Localized injections do not address system-wide issues
- Has potential to permanently eliminate the problem, but long-term side effects are still unknown

# Small Molecule Development

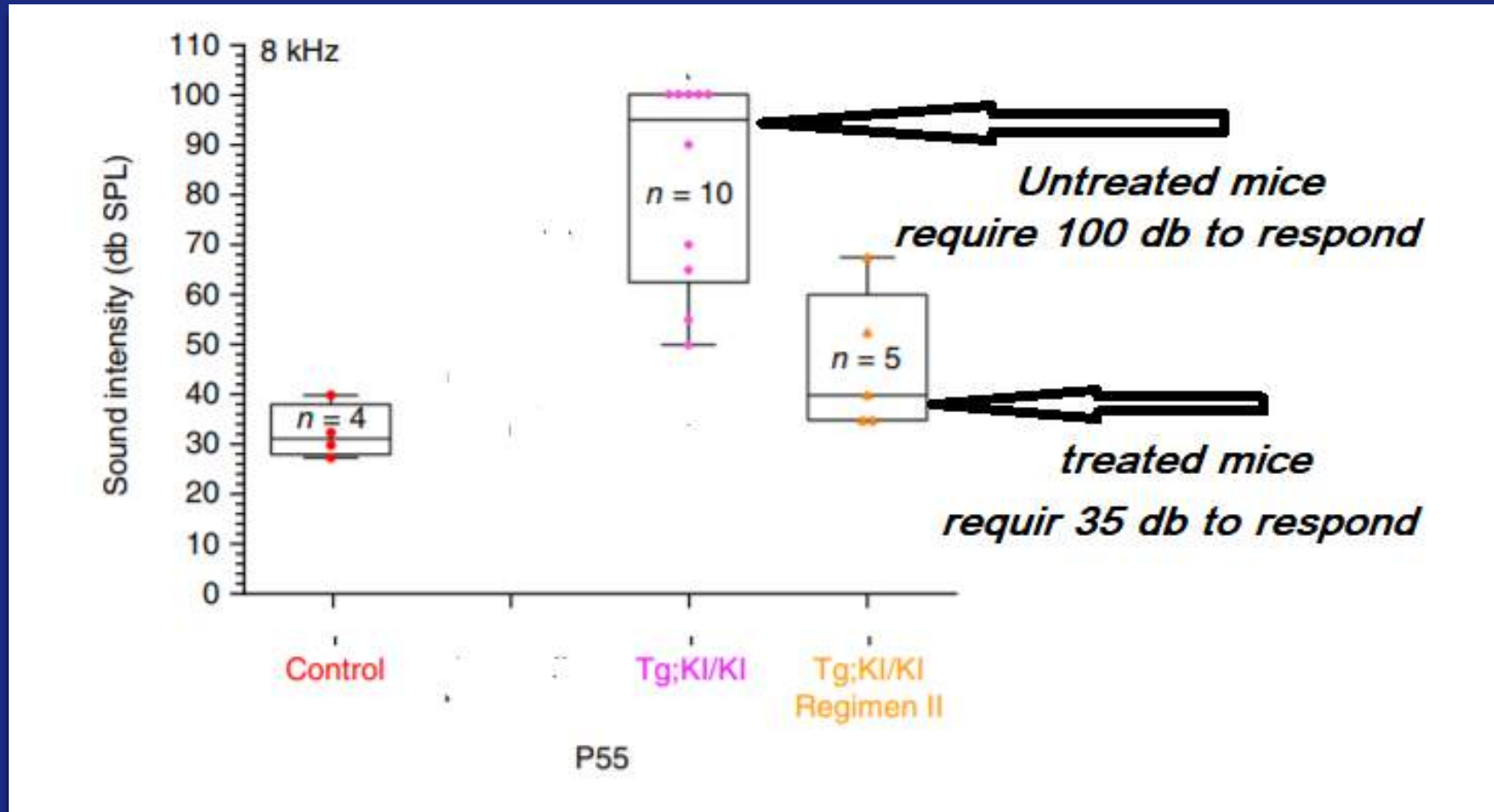
- First developed beginning in 1928 with the discovery of penicillin
- Has been used to develop countless drugs in circulation today
- There is significant precedent for the pathway to gaining regulatory approval and determining clinical safety
- When translated into drug therapies, small molecules can often be administered orally

# BF844—Our Novel Compound



- A protein stabilizer with selectivity for *CLRN1*
- Identified via a high throughput screening of over 5,000 molecules
- Impact on hearing loss was measured using the auditory evoked brain responses in transgenic mice
- BF844 was administered intraperitoneally once daily at 30 mg/kg
- Mice were observed at postnatal days 22, 46 and 55

# BF844 was Effective in Mitigating Hearing Loss in USH3 Mouse Model



# The Benefits of BF844

- Restored the auditory sensitivity of USH3 mice to the same decibel level as healthy mice
- Designed as systemic treatment to address both sensory losses
- Rescues mutations in rhodopsin
- Administered orally
- Crosses blood-cochlear and blood-retinal barriers

# Clinicians on our Board of Directors

## **Dr. David Saperstein, M.D.**

Partner Physician, Proliance Retina; Co-Founder & Chief Medical Officer, Retinagenix; Co-Founder & CEO, Zumedix, LP

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## **Dr. Julia Hayes, M.D.**

Medical Oncologist, Dana-Farber Cancer Institute, St. Elizabeth Medical Center; Assistant Professor in Medicine, Harvard Medical School



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**Dr. Eeva-Marja Sankila, M.D., Ph.D.**

Clinical Consultant in Ophthalmology, Blueprint Genetics

# Next Steps

- Complete remaining toxicity tests prior to IND submission
- Scale up material production to meet GMP standards
- Design clinical trials
- On average it costs \$2 billion dollars to develop a small molecule into a drug therapy

# What You Can Do

- Get genotyped and register with the Usher Coalition
- Support our research
- Sign up for clinical trials
- Get in touch with us by emailing [georgia@usheriii.org](mailto:georgia@usheriii.org)

**We want to connect with you!**

# Learn More

To learn more about USH3 and the Initiative, please visit our website [www.usheriii.org](http://www.usheriii.org), where you can read articles and interviews, get involved, and donate directly to USH3 research

Thank you to our incredible staff: **Dr. Mahdi Farhan** (Chief Scientific Officer); **Tracey Fletcher**, (General Counsel and Managing Director) and **Georgia Horn** (Development Director and Project Manager)