Usher syndrome
Close to a cure?

The Path to Clinical Trials

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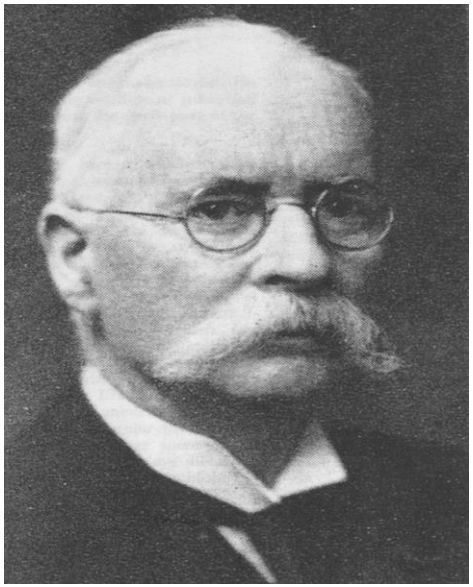
A cure?

- Early diagnosis is the key

Usher syndrome
Definition

- Defined as hearing loss with retinitis pigmentosa in the absence of other significant symptoms.
- It is inherited as an autosomal recessive.
- There are three clinical types.
- There are at least twelve genes involved



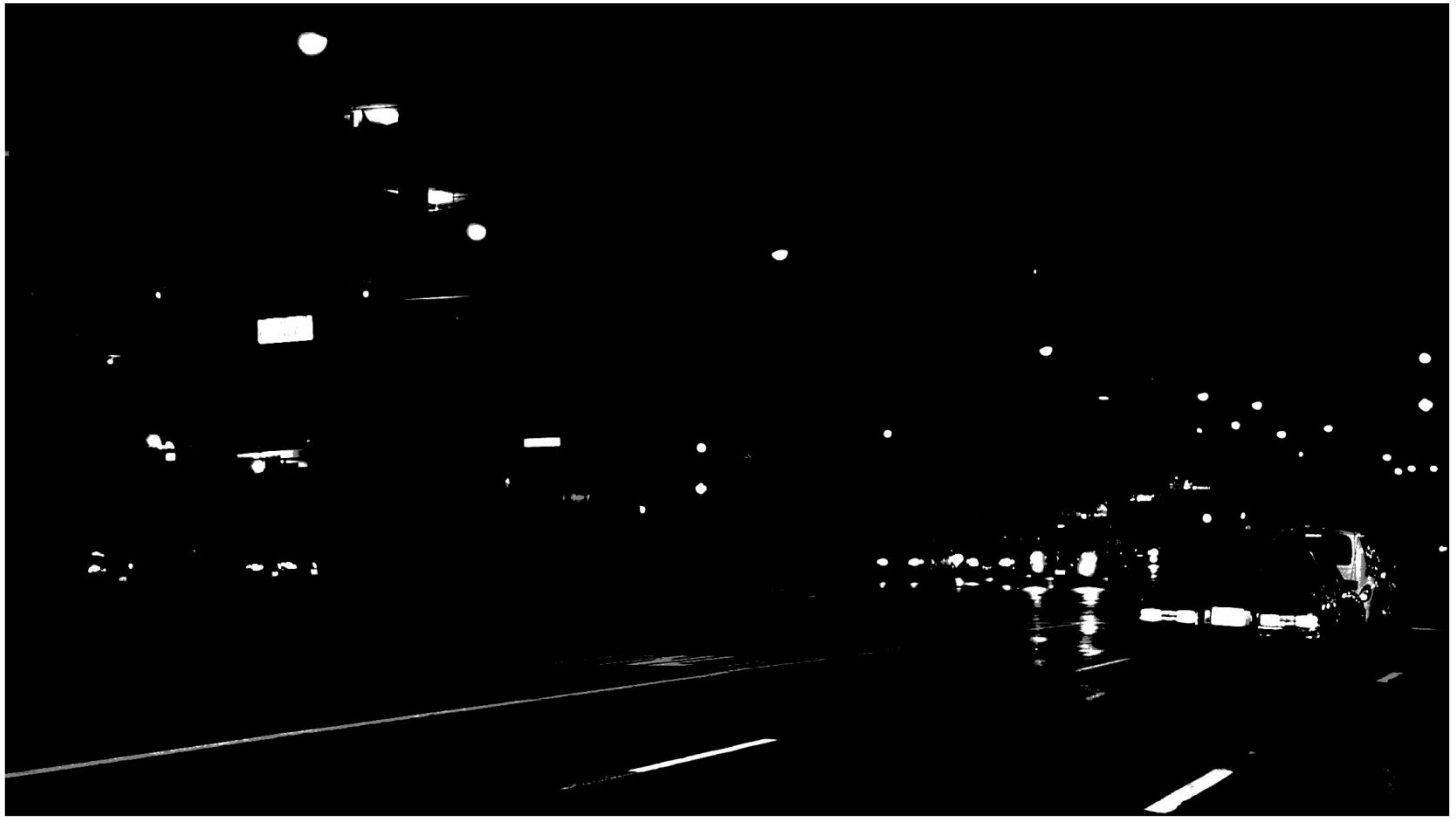
Dr. Charles H. Usher

Clinical Types

- Type 1:
  - Profound hearing loss (deaf).
  - Early onset RP.
  - Balance problems.
- Type 2:
  - Moderate to severe hearing loss (hard of hearing)
  - RP evident in their teens
  - No balance problems
- Type 3:
  - Progressive hearing loss.
  - Looks like type 2 as children.
  - Looks like type 1 as older adults.
- Atypical
  - Doesn’t fit any of the first three categories.

What we see

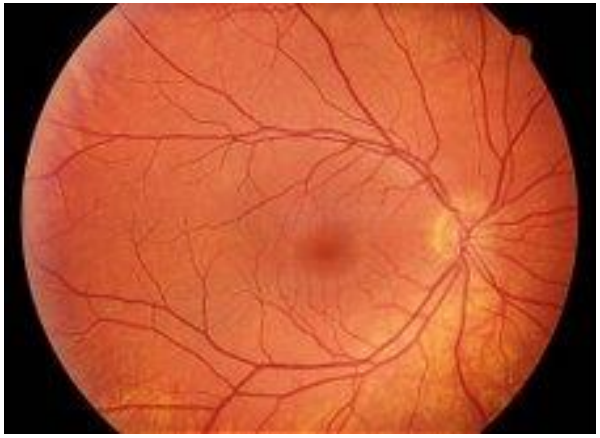
What an Usher person sees

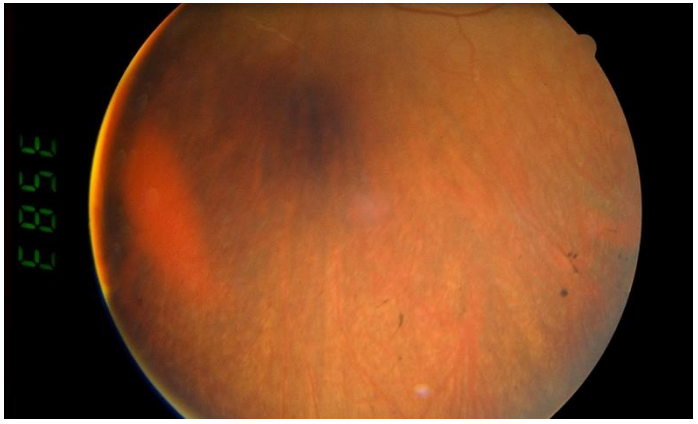


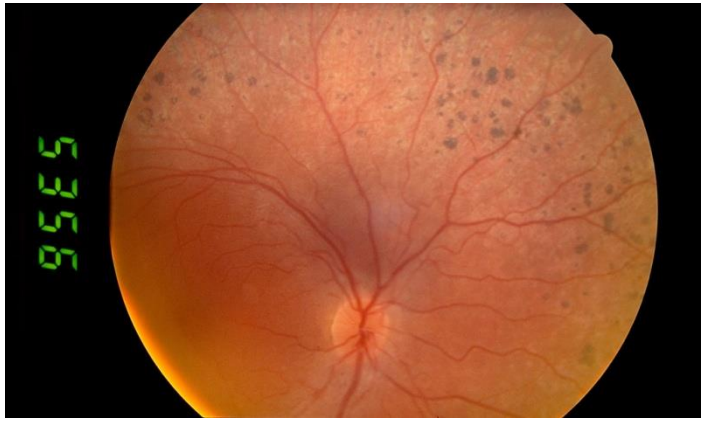
The way most of us see it.
The old Iowa Capitol building

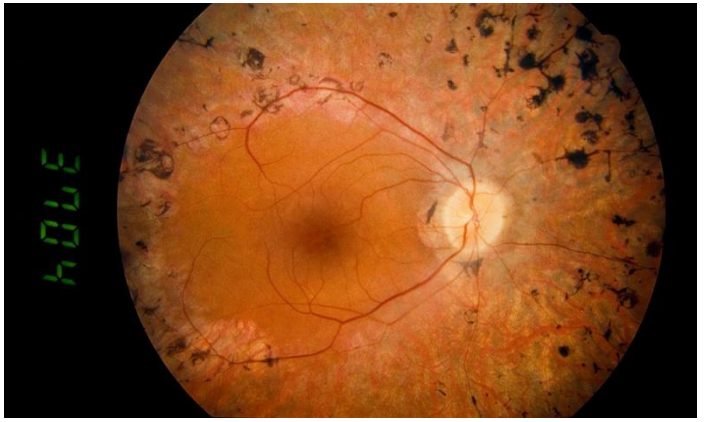
Usher at 18 to 30 years

Usher Retinitis Pigmentosa Stages



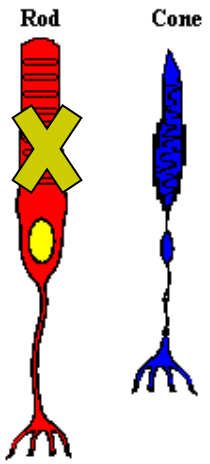




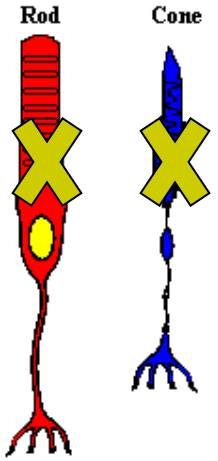


Why do people with Usher really go 'blind'?

- Rod disease → loss of rod function → nightblindness and tunnel vision.



- Loss of rods → fragile retina → loss of cones (central vision), macular edema, cataracts → blindness.



<u>Path to Blindness is a multistep process</u>

What do we want to do with Usher syndrome?

1. Slow or Halt the neurosensory degeneration, or
2. Restore damaged neurosensory cells, or
3. Replace dead neurosensory cells

Seven Steps to a Treatment for an Inherited Disease

1. **Find the disease gene(s)**
2. Correlate genotypes with phenotypes
3. Find or develop animal models
4. Elucidate the disease mechanism
5. Find or develop an effective treatment in the animal model
6. Screen the human population to identify people who might benefit
7. Test the treatment in these people

There are >11 Genes involved

- Usher Type I
  - Usher 1b: MYO7A
  - Usher 1c: Harmonin
  - Usher 1d: CDH23
  - Usher 1f: PCDH15
  - Usher 1g: Sans
- Usher type II and III
  - Usher 2a: Usherin
  - Usher 2c: VLGR1
  - Usher 2d: Whirlin
  - Usher 3a: Clarin-1

There are two others recognized through linkage (Usher Ie and 1h)

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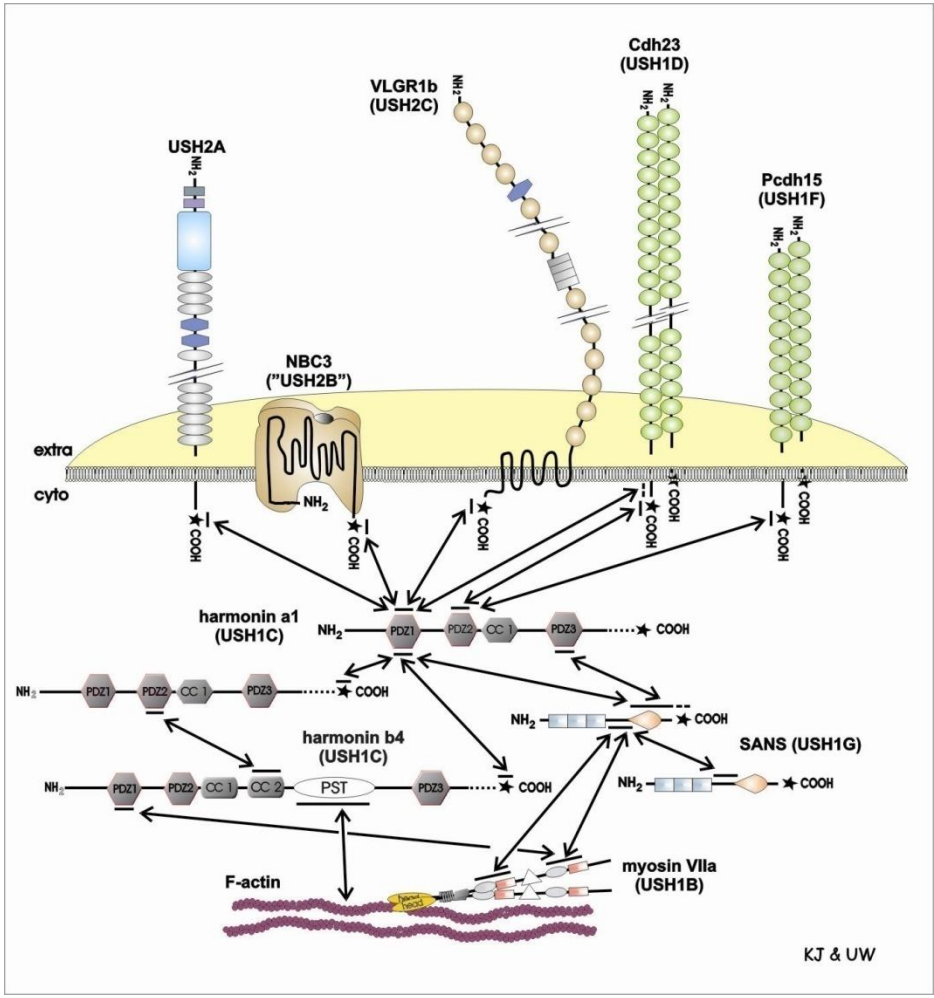
Usher syndrome interactome as proposed by Uwe Wolfrum

- The function of the interactome is unclear.
- Structural in the cochlea?
  - Tip and ankle links
- Cargo transport in the retina?



Usher interactome

- Complex machinery.
- Like a construction crane?
- Cargo transport?

Knowledge of the interaction of the Usher proteins gives us an advantage when thinking of possible therapies.

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How frequent is Usher syndrome?

- 4.4 per 100,000 (Boughman, 1983)
  - USA
- 3.6 per 100,000 (Groendahl and Mjoen, 1983)
  - Scandinavia
- >50 studies in the 20th century of schools for the deaf indicate about 1/20 with retinitis pigmentosa
  - Throughout the world
- **All previous studies focused on the deaf (i.e. profound hearing loss) and used data from schools for the deaf and were phenotypically driven.**

ARTICLE

Frequency of Usher syndrome in two pediatric populations: Implications for genetic screening of deaf and hard of hearing children

William J. Kimberling, PhD[1,2], Michael S. Hildebrand, MD[1], Aiden E. Shearer[1], Maren L. Jensen, BS[1], Jennifer A. Halder, BS[2], Karmen Trzupek, MS, Edward S. Cohn, MD[1], Richard G. Weleber, MD[4], Edwin M. Stone, MD, PhD[2], and Richard J. H. Smith, MD, PhD[1]

- 15 to 18% of deaf and hard of hearing children have a genotype suggestive of Usher syndrome.
- Frequency of Usher genotypes in the general population is 1 in 6500
- About 45,000 Americans have a form or Usher syndrome

Genetics in Medicine, 2010, in press

Accrual is often the most critical issue in the design of clinical trials.

Orphan diseases are especially problematic.

For example – There are no more than 85 individuals in the USA with Usher 3a due to c.144T>G,p.N48K, the most prevalent Jewish mutation

Key Components of Our Testing Strategy

1) An inexpensive assay that targets common mutations.
2) Probability-driven DNA sequencing for rare and/or novel alleles.
3) An evidence based algorithm to know when to stop testing.

Tier 1 Usher Testing
Screening stage

- Tier 1 (Screening)
  - Uses Fluidigm platform.
  - 40% sensitivity and increasing.
  - Suitable for:
    - screening children with hearing loss.
    - patients with a clinical diagnosis of Usher syndrome.
  - Cost = 187 USD

- www.carverlab.org

Usher Testing
In Depth Stage

- Tier 2 (Testing In depth)
  - Uses Standard Sequencing.
  - 80% sensitivity.
  - Suitable for:
    - Hearing loss children with only 1 mutation at Tier 1
    - All Usher patients not resolved at Tier 1
  - Cost is $200 to $500
- Tier 3 (Research)
  - Uses Next Generation Sequencing
  - ?100%? Sensitivity
  - Suitable for ALL who are not resolved by tier 2 testing.
  - Cost is $1500 to $4500 and dropping

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What is an outcome measure?

- A measure the success or failure of a certain treatment.
- A good outcome measure:
  - Relates to the disease process.
  - Is safe.
  - Is cost effective.
  - Will provide evidence in a reasonable time frame.

How does natural history relate to outcome measures?

- Lets us know which outcome measures are the best suited to the immediate purpose.
- Gives important pretrial information that can be used to design the clinical trial:
  - Predict the number of subjects needed.
  - Predict what endpoint must be reached for termination.
  - Justify safety issues.
- Without such information, the clinical trial is unlikely to receive the needed funding!

Why diagnose Usher syndrome early?

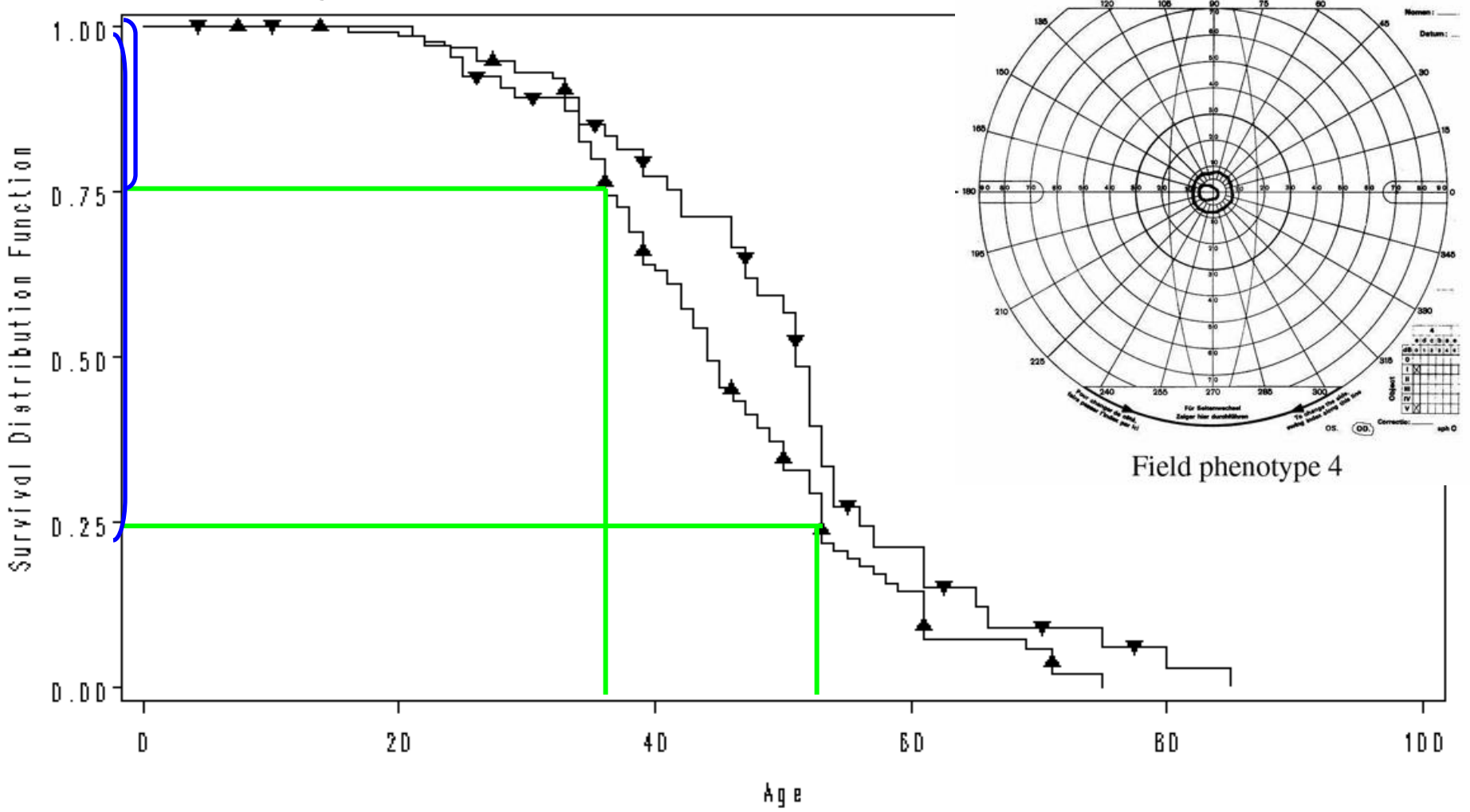
- Genetic counseling
- Education and Safety
- Clinical Issues
- Current Therapy
- Clinical trials

Early diagnosis is key to treatment!

Children and Clinical Trials

- The distribution of vision decay is a sigmoid with an apparent rapid decline phase that occurs before adulthood.
- The time course of decay will depend upon:
  - Type of Usher {gene and mutation}
  - The outcome measures used.
- **The challenge will be to define the best outcome measure for the right age and genotype**.

Survival analysis- visual field –The likelihood of having >5 deg



Field phenotype 4

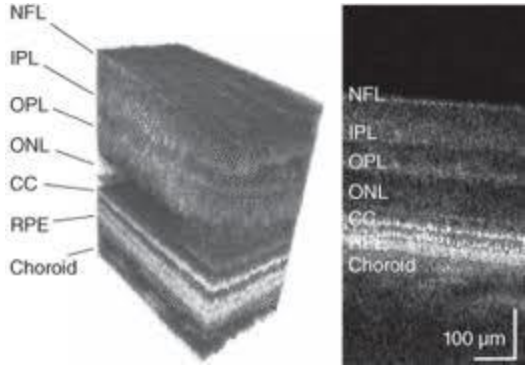
Usher type I

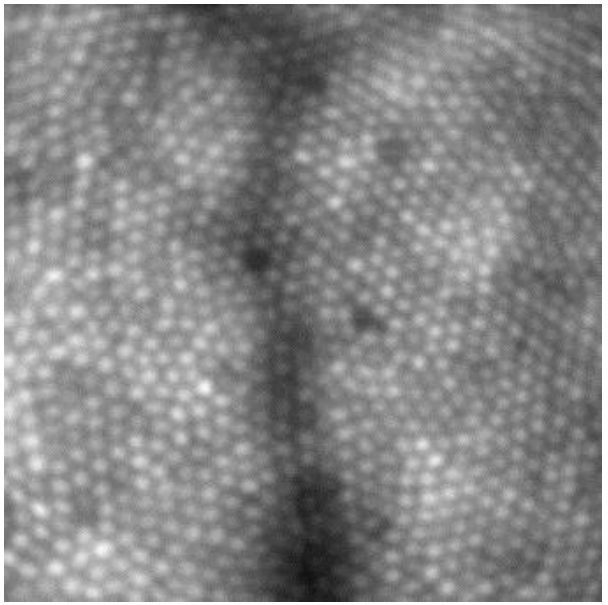
Usher type II

($p<0.05$)

Potential Outcome Measures

- Vision
  - Electroretinogram - ERG
  - Static and Kinetic Perimetries
  - OCT – optical coherence tomography
  - Adaptive Optics
  - Automated Fundus Analysis
  - Pupillometry
- Hearing and Balance
  - Audiology
  - OAE
  - ABR
  - Vestibular Testing





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Can Usher syndrome be treated?

- **Safety and geographic orientation**
- **Life style changes**
  - **Smoking cessation**
  - **Sunglasses**
  - **Diet**
- **Vitamin supplementation and antioxidants**
- Prosthetics
  - **Cochlear Implants**
  - Retinal Implants
- CNTF and other growth factors
- Aminoglycoside look alikes.
- Stem Cell Therapy
- Gene therapy

Prosthetic devices

- Cochlear implant
  - Well established
  - Successful for Usher

- Retinal implant
  - Developing technology
  - Clinical trials begun but NOT for Usher

Anti-oxidants may slow progression of RP?

- Animal models are suggestive.
- Shown helpful in macular degeneration.
- Several antioxidants available:
  - Vitamin E, Vitamin C, alpha-lipoic acid, Saffron, TUDCA, …

Vitamin A supplementation may slow the progression of RP

- Harvard medical school.
- First study reported Vitamin A slowed the progression of RP.
- **Later study showed a greater effect when in combination with diet (fish important).**
- BUT, it remains controversial.

+

Prevention may be as simple as wearing sunglasses

Animal studies suggest that light (uv and blue) accelerates the loss of rods and is especially damaging to Usher retinas

Unproven in humans

Depending upon the frequencies, filtering lasses may be appropriate even indoors.

Certain mutations may be specifically treatable

Readthrough of dystrophin stop codon mutations induced by aminoglycosides

Michael T. Howard PhD[1], Christine B. Anderson BS[1], Uwe Fass PhD[1], Shikha Khatri MS[1], Raymond F. Gesteland PhD[1], John F. Atkins ScD[1], Kevin M. Flanigan MD[1,2,*]

Article first published online: 23 JAN 2004

DOI: 10.1002/ana.20052

Issue

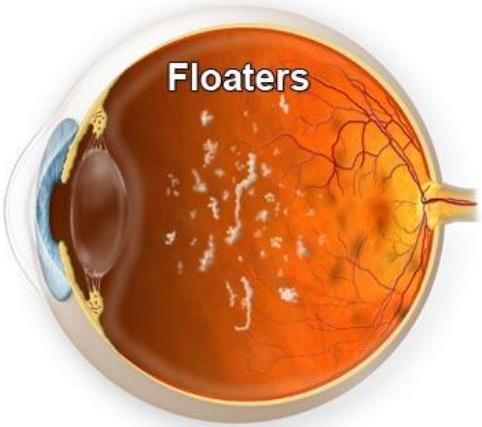
Annals of Neurology

Volume 55, Issue 3, pages 422–426, March 2004

- *Stop* mutations are like periods.
- Certain drugs can force the cell to read through false ‘periods’.
- Only about 10% of all Usher mutations are *stops*.

Is Retinitis really and ‘itis’

- Home front observation: Older Usher patients have floating objects in the retina. Are these macrophages?
- Would **anti-inflammatory drugs** slow the progression to the second stage of retinal dystrophy, that is, involvement of the macular and central vision?
- Glybina IV, Kennedy A, Ashton P, Abrams GW, Iezzi R. (2009) **Photoreceptor neuroprotection in RCS rats via low-dose intravitreal sustained-delivery of fluocinolone acetonide.** Invest Ophthalmol Vis Sci. 50:4847-57.



Therapies for Usher syndrome
CNTF

- CNTF = Ciliary neurotropic factor
  - Neuroprotective
- **Novel delivery**
  - **Encapsulated cells genetically programmed to make CNTF**
  - **Inserted within the vitreous**
- Phase I clinical trial completed.
  - Sieving et al., (2006) **PNAS** *Ciliary neurotrophic factor (CNTF) for human retinal degeneration: phase I trial of CNTF delivered by encapsulated cell intraocular implants.*
  - Safety demonstrated
  - Some indication that vision improved.
- Phase II clinical trials underway.

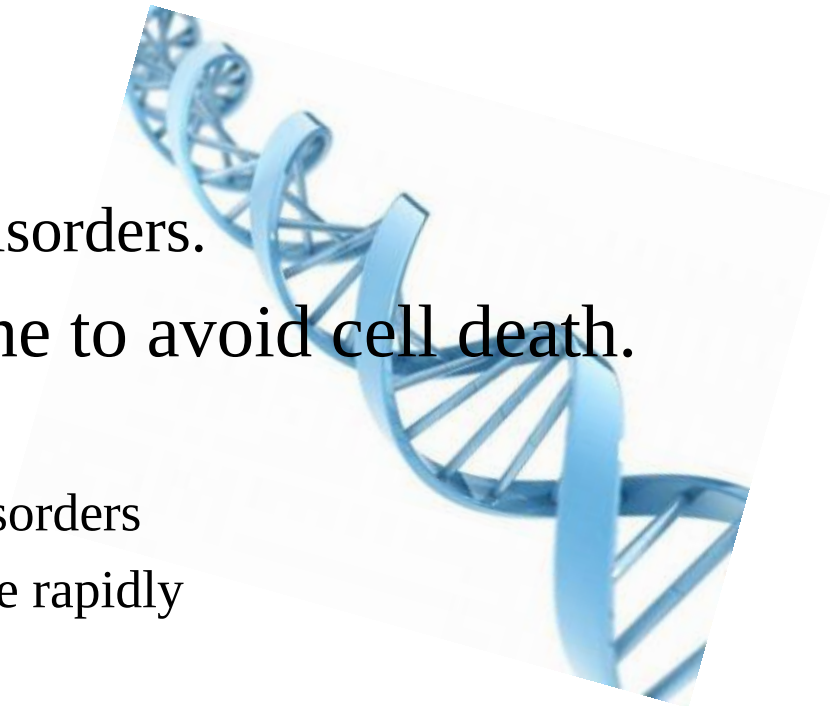
How does CNTF delivery work?

Gene therapy will be the gold standard or treatment

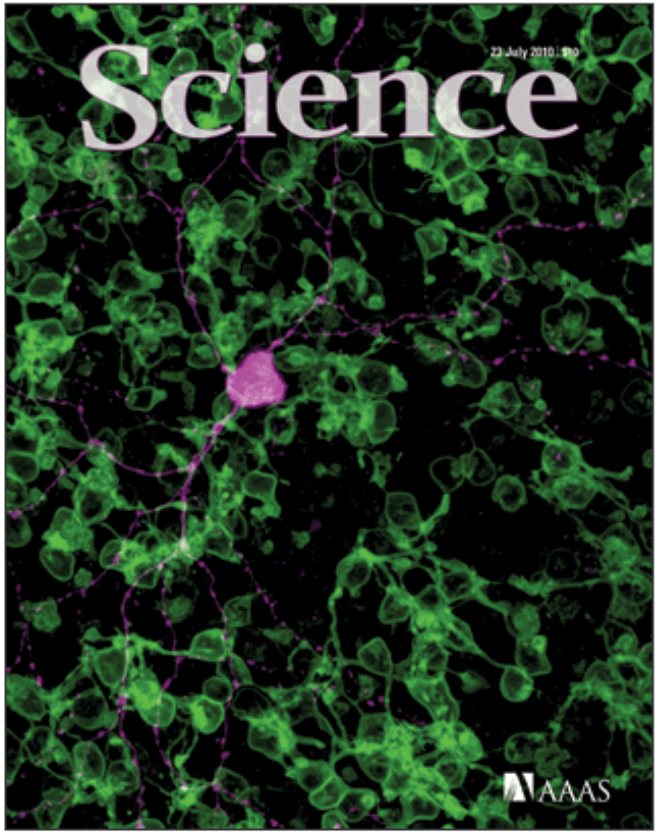
- Genes are information.
- When a gene is ‘knocked out’, the information is cell needs is missing.
- To correct the problem, the functional gene must be delivered to the cells that need to use that information
- Other non-gene based therapies may factor into success.

Gene Therapy
Two General Approaches

- Replacement Therapy: Replace the defective gene:
  - Gene specific
    - Limited patient population
    - Clinical trials will be slow
  - Limited mostly to recessive disorders.
- Addition Therapy: Add a gene to avoid cell death.
  - Not gene specific
    - Broad benefit across several disorders
    - Clinical trials will proceed more rapidly



Gene Addition Therapy Research Holds Promise



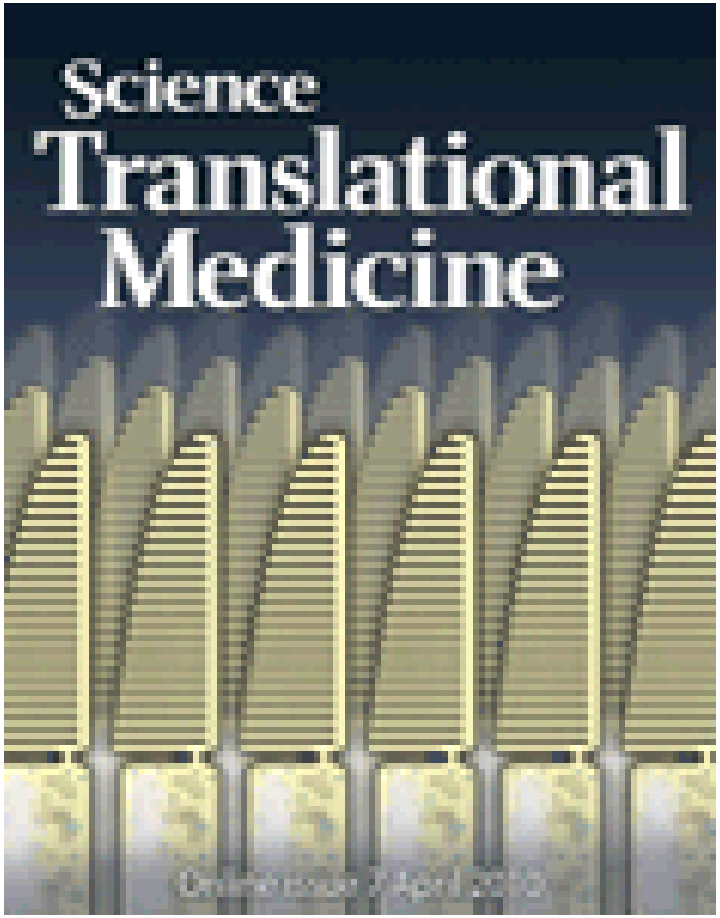
COVER Retinal photoreceptors from a mouse model of retinitis pigmentosa, a degenerative disease that leads to blindness, following gene therapy. Expression of a microbial light-activated ion pump (green) in damaged cone cells restored light sensitivity to the diseased retinas. An activated ganglion cell, which relays visual information to the brain, is shown in magenta (diameter, ~12 μm). See page 413. Image: Volker Busskamp and Botond Roska/Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland

Insertion of a gene to alter the ionic pumping of the cone cells

Gene therapy restored light sensitivity to the cones of an animal model with RP.

Busskamp, Science, July 2010

Another idea about Gene Addition Therapy



- Rods: Peripheral vision and night vision.
- Cones: Central vision, fine detail, color.
- Rods make a factor that keeps Cones healthy
- This factor slows RP in an animal model.

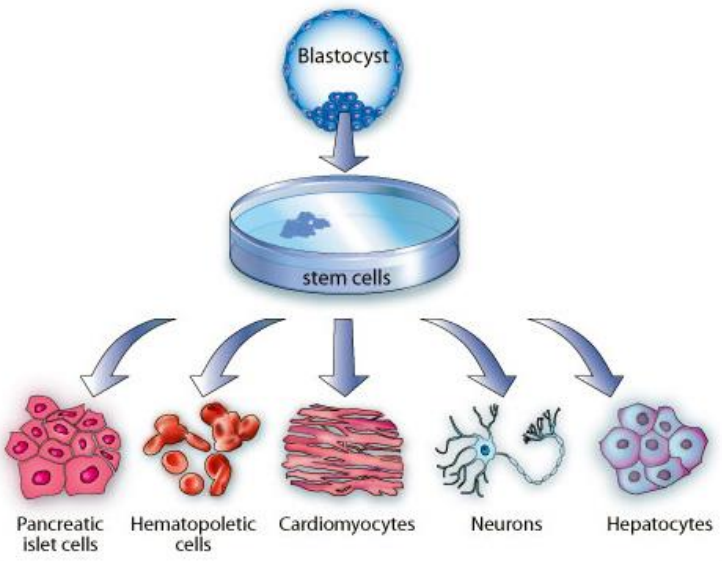
Rod-Derived Cone Viability Factor for Treating Blinding Diseases: From Clinic to Redox Signaling Thierry Léveillard and José-Alain Sahel *Sci Transl Med 7 April 2010*

Gene therapy and the future

- Lancelot, the Briard Dog
  - Leber's congenital amaurosis, a severe juvenile RP.
- Gene (RPE65) inserted via a viral vector in one eye.
  - Acland, et al., (2005) **Mol. Ther.** *Long-term restoration of rod and cone vision by single dose rAAV-mediated gene transfer to the retina in a canine model of childhood blindness.*
- **Gene therapy programs are now underway for Usher 1b, 1c, 1d, 2a, and 3a**
- **A phase 1/2 clinical trial has started in Oregon for Usher 1B**

Stem cell therapy

- Replace dead cells.
- Requires good knowledge of developmental triggers.
- Could lead to organ engineering.
- Immune response is still and issue.
- Can be used in combination with gene therapy.



The Point

There are many good ideas about treatments for children and adults with Usher syndrome.

These ideas must be tested by clinical trials before they can be used confidently.

The problem

- A major problem with clinical trials for orphan disorders like Usher is the availability of suitable subjects.
- No hints from epidemiologic and natural history studies. More research is needed here.
- Few clinical trials have been attempted involving Usher syndrome. None have targeted children.

Where do we go from here?

- Increased governmental and private support will be needed to translate all that has been learned into a real benefit for individuals and families with Usher syndrome.

Epidemiology, natural history studies, genotype/phenotype studies, molecular mechanism studies, psychosocial studies. genetics, improve technologies, animal models, and

Clinical Trials

Support From:

- National Institute for Deafness and Communication Disorders
- Foundation Fighting Blindness.
- National Eye Institute.
- National Institute for Child Health and Development.
- Boys Town Research Hospital
- Howard Hughes Medical Institute.
- Hear See Hope Foundation.
- Decibels foundation
- Usher 3 Consortium
- And all the Usher people and their families.

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