USHER III INITIATIVE

USHER SYNDROME COALITION

Usher III Initiative – Current Research and Objectives

A presentation for the Usher Syndrome Coalition

By David Saperstein, Scientific Director

March 9, 2015

Usher III Initiative

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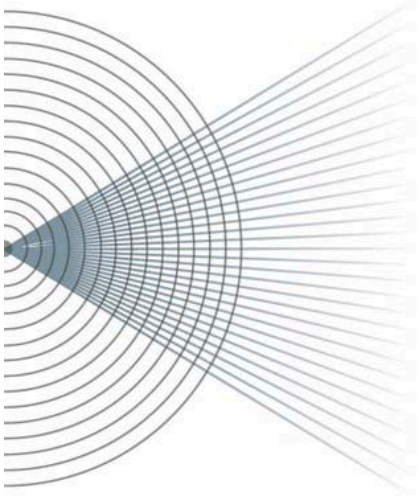
- Founded by Richard and Cynthia Elden in 2007
- First to specifically fund Usher III Research
- Collaborative, Treatment Directed and Orchestrated Research to find treatments for vision loss in Usher III disease



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DEDICATED TO DEVELOPING
CURES FOR BLINDNESS

What is Usher Syndrome, Type IIIa?

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- Post-lingual hearing loss and retinal degeneration
- Diagnosed in the first decade of life
- Initially milder defects, but become more severe in the 3rd and 4th decades
- 5th decade both hearing and vision are profoundly affected.

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What Causes Usher Syndrome, Type IIIa?

- Autosomal recessive
- Defects in the Clarin 1 gene
- What is Clarin 1? Membrane-bound tetraspanin

Ush IIIa: Prevalence

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- 2000 people in US and Europe

Ush IIIa: Prevalence

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- 2000 people in US and Europe

- Finland

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Ush IIIa: Prevalence

- 2000 people in US and Europe
- Finland
- Ashkenazi Jews

Ush IIIa: Prevalence

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- 2000 people in US and Europe
- Finland
- Ashkenazi Jews
- The prevalence in Eastern Europe and Asia are unknown at this time

Current Treatment – Hearing Loss

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- Hearing aids

- Cochlear implants

Current Treatment – Vision Loss

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- Visual Aids
- Vision Training
- Orientation and mobility

Current Treatment – Vision Loss

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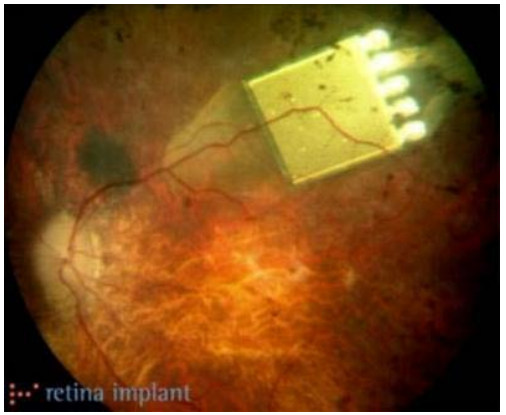
- Retina Prostheses



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Typical Research Model

- Request
- Evaluate
- Fund
- 1-2 yrs
- re-evaluate

Usher III Research Model

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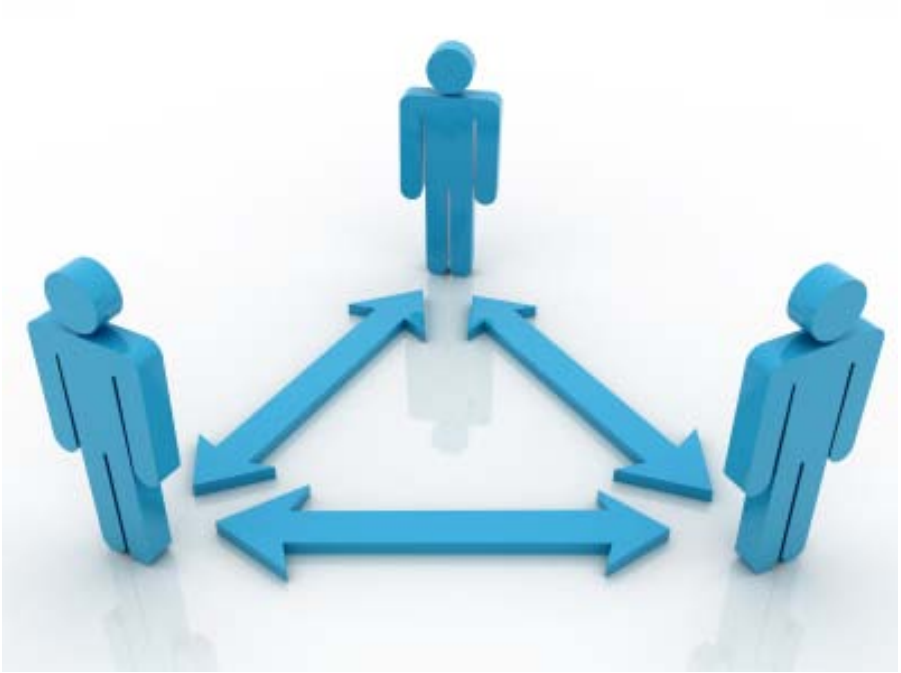
- Identify
- Entice
- Collaborate
- Facilitate
- Orchestrate



Who are we?

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Board of Directors

Richard Elden

Cynthia Elden

Frank C. Meyer

Samir Patel, M.D.
Founder and Chief Medical Officer
Ophthotech Corporation

Paul Sternberg, Jr., M.D.
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William Harte, Ph.D.
Director of Pharmaceutical Development

Lindsey J. Whyte
Project Manager

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Research Labs

Case Western Reserve University

Yoshikazu Imanishi, Ph.D.
Department of Pharmacology
Assistant Professor

Dr. Kumar Alagramam
Department of Otolaryngology
Associate Professor
Director of Research

University of California, San Francisco

Dr. Lawrence Lustig*
Department of Otolaryngology
Professor of Otolaryngology/Head and Neck Surgery

University of Florida, Gainesville

Dr. William W. Hauswirth, Ph.D.
Maida and Morris Rybaczki Eminent Scholar Chair in Ophthalmic Sciences

* Effective July 2014 Dr. Lustig is the Chair of the Department of Otolaryngology/Head and Neck Surgery at the Columbia University College of Physicians and Surgeons and otolaryngologist-in-chief at New York-Presbyterian/Columbia University Medical Center

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Ush IIIa: Basic Questions

- What does Clarin1 do?
  - Biochemistry
- What happens when it is defective?
  - Molecular biology
  - Mouse Models

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Clarin1

- Very little protein in the eye and ear
- Present in infant and adult
- Membrane bound
- Association with other Usher proteins?

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Mouse Models

- Mice with defective Clarin1 rapidly go deaf

- Mice have no vision deficit

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Therapeutic Approaches

- Gene Replacement Therapy
  - Eye
  - Ear
- Small Molecule Chaperone Therapy

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Retinal Gene Therapy

- Technically straight forward

PROBLEM

- No retinal degeneration
- High levels of Clarin1 are toxic

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Retinal Gene Therapy

SOLUTION

- Modify delivery methods to eliminate toxicity
- Refine animal models so their retinas degenerate

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Cochlear Gene Therapy

PROBLEM

- Technically very difficult
- Mice lose hearing too fast

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Cochlear Gene Therapy

SOLUTION

- Lustig Laboratory (UCSF/Columbia)
- Create a mouse with delayed hearing loss

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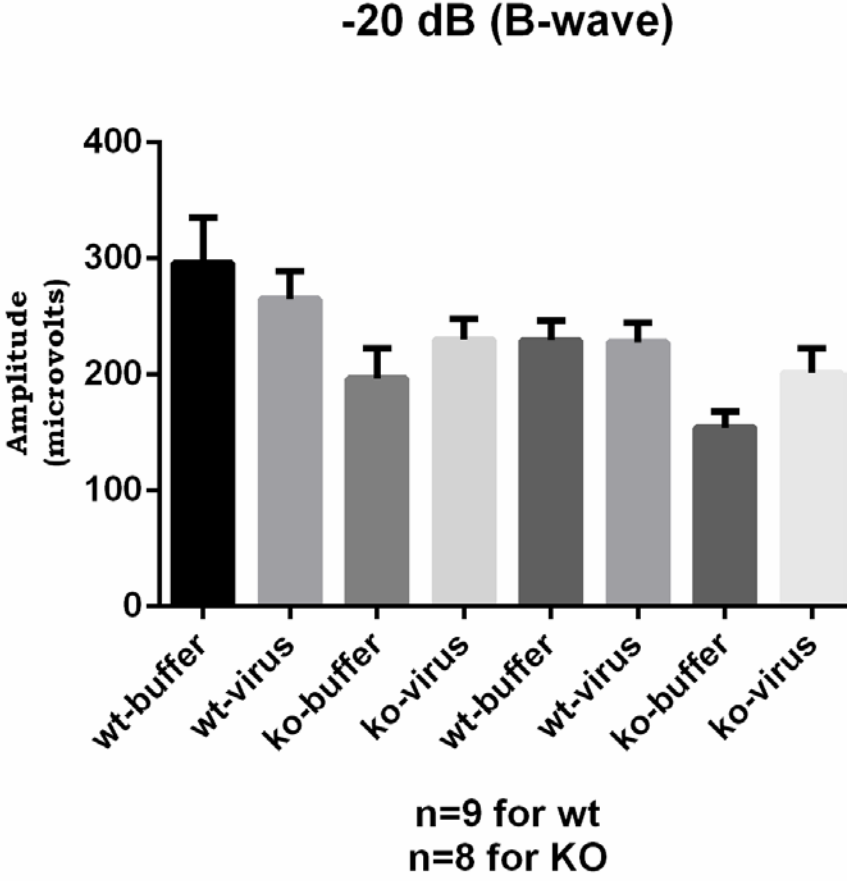
Retinal Gene Therapy Results

Preliminary data

- Treated with modified viral vector
- Delayed ERG loss in treated animals



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Cochlear Gene Therapy Results

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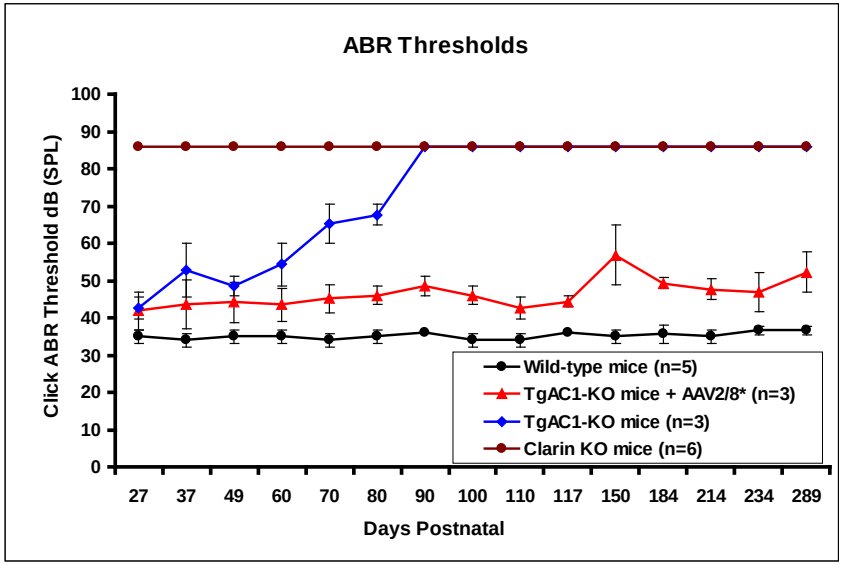

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Small Molecule Chaperone Therapy for the N48K mutation in Usher IIIa

- Ashkenazi Jewish population
- N48K mutation in the Clarin 1 gene.
- Protein is made and then is immediately degraded

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Small Molecule Selection and Optimization

- We discovered an approved drug that prevents degradation
- The drug is too toxic
- Developed and assay using the toxic drug to screen for other potential compounds

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High Throughput Screening

- Screen several hundred thousand compounds in a few weeks.

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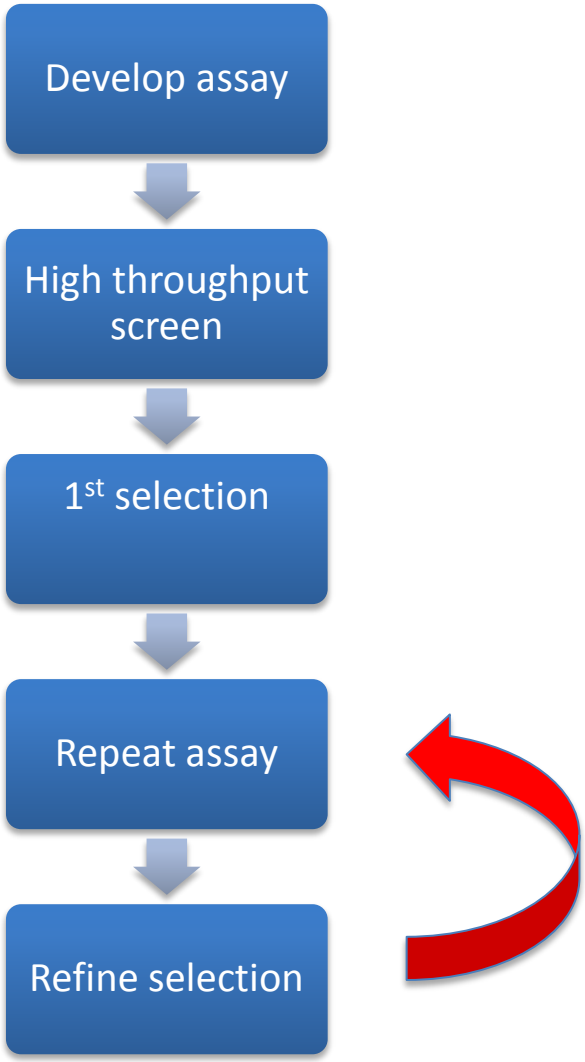
High Throughput Screening



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Small Molecule Therapy for Hearing Loss

- Usher III mice with delayed hearing loss
- Daily dosing of the Ush3 compound

- Robust statistically significant reduction in hearing loss

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Small Molecule Therapy for the Retina

PROBLEM

- No retinal degeneration in mice with N48K mutations
- No way to prove if it works or not in animals

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Next Steps – Retinal and Cochlear Gene Therapy

- Further animal experiments to refine vector and dosing
- Develop Pharmaceutical development plan
- Find Pharma partner to bring to clinic

Next Steps – Small Molecule Therapy

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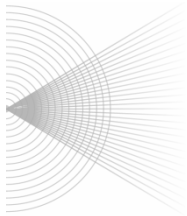
- Find other potential uses
- Develop Pharmaceutical development plan
- Find Pharma partner to bring to clinic



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Thank You

Questions