Usher III Initiative – Current Research and Objectives

A presentation for the Usher Syndrome Coalition
By David Saperstein, Scientific Director
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Usher III Initiative

- 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
What is Usher Syndrome, Type IIIa?

- 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.
What Causes Usher Syndrome, Type IIIa?

- Autosomal recessive
- Defects in the Clarin 1 gene
- What is Clarin 1? Membrane-bound tetraspanin
Ush IIIa: Prevalence

- 2000 people in US and Europe
Ush IIIa: Prevalence

- 2000 people in US and Europe
- Finland
Ush Illa: Prevalence

- 2000 people in US and Europe
- Finland
- Ashkenazi Jews
Ush IIIa: Prevalence

- 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

- Hearing aids

- Cochlear implants
Current Treatment – Vision Loss

- Visual Aids
- Vision Training
- Orientation and mobility
Current Treatment – Vision Loss

- Retina Prostheses
Typical Research Model

- Request
- Evaluate
- Fund
- 1-2 yrs
- re-evaluate
Usher III Research Model

- Identify
- Entice
- Collaborate
- Facilitate
- Orchestrate
Who are we?

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Professor of Otolaryngology/Head and Neck Surgery

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* 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
Ush Illa: Basic Questions

• What does Clarin1 do?
  – Biochemistry

• What happens when it is defective?
  – Molecular biology
  – Mouse Models
Clarin1

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

• Mice with defective Clarin1 rapidly go deaf

• Mice have no vision deficit
Therapeutic Approaches

• Gene Replacement Therapy
  – Eye
  – Ear

• Small Molecule Chaperone Therapy
Retinal Gene Therapy

• Technically straightforward

PROBLEM

• No retinal degeneration
• High levels of Clarin1 are toxic
Retinal Gene Therapy

SOLUTION

• Modify delivery methods to eliminate toxicity

• Refine animal models so their retinas degenerate
Cochlear Gene Therapy

PROBLEM

- Technically very difficult
- Mice lose hearing too fast
Cochlear Gene Therapy

SOLUTION

- Lustig Laboratory (UCSF/Columbia)
- Create a mouse with delayed hearing loss
Retinal Gene Therapy Results

Preliminary data

• Treated with modified viral vector

• Delayed ERG loss in treated animals
Cochlear Gene Therapy Results

Preliminary data

- Treated with modified viral vector

- Delayed ERG loss in treated animals
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
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
High Throughput Screening

- Screen several hundred thousand compounds in a few weeks.
High Throughput Screening

1. Develop assay
2. High throughput screen
3. 1st selection
4. Repeat assay
5. Refine selection

Flowchart: Develop assay → High throughput screen → 1st selection → Repeat assay → Refine selection → 1st selection
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
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
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

• Find other potential uses

• Develop Pharmaceutical development plan

• Find Pharma partner to bring to clinic
Thank You

Questions