Curing Usher Syndrome

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Financial Disclosures

NONE
Realistic

HOPE
Realistic

HOPE

1) Plans that will work
2) A committed team
Three Questions

• When?
• But, what if . . . ?
• How close are we?
When?
When?

As soon as humanly possible.
But, what if . . . ?
But, what if . . . ?

We will fix it.
How close are we?
Close enough to walk!
What will success look like?
What will success look like?
Case Report

- 14 year old twins
- Hearing loss noticed as newborns
- Bilateral cochlear implants
- 20/25
- Some difficulty in dim light
Case Report

• Clinical diagnosis: Type I Usher Syndrome
Case Report

- Clinical diagnosis: Type I Usher Syndrome
- Molecular Test: $575
Case Report

- Clinical diagnosis: Type I Usher Syndrome
- Molecular Test: $575
- Result: **USH1C**
  Val72Val (splice variant), Thr78insC
Project Usher

www.projectusher.org
Steven W. Dezii Research Facility
Cost?

Less than $20,000 (including ten years of follow up).
What will success look like?
Case Report

• 59 year old woman

• Hearing loss noticed in early childhood (hearing aids)

• RP discovered at age 15

• Now sees only “hand motions” in both eyes
We need to:

- Skin -> stem cells -> retinal cells
- Dissolvable polymer support
- Transplanted into the subretinal space of the macula
Keratinocytes

400 µm
Keratinocytes

Isolated iPSCs

400 µm
iPS cells → EB formation → RPC differentiation → Photoreceptor production

**D1**
- 5 Days
- EB media +1ng/ml Dkk1, +1ng/ml Noggin +0.5ng/ml bFGF

**D5**
- 10 Days
- DF media 1 +10ng/ml Dkk1, +10ng/ml Noggin, +10ng/ml Igf1, +10ng/ml bFGF

**D15**
- 5 Days
- DF media 2 +10ng/ml Dkk1 +10ng/ml Noggin +10ng/ml Igf1 +10ng/ml bFGF 10mM DAPT

**D21**
- 10 Days
- DF media 3 +10ng/ml Dkk1 +10ng/ml Noggin +10ng/ml Igf1 +10ng/ml bFGF +10mM DAPT +2ng/ml aFGF

**D30**
- 120 Days
- DF media 4

**D150**

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200 µm

45 days
iPS cells → EB formation

EB media +1ng/ml Dkk1, +1ng/ml Noggin +0.5ng/ml bFGF (D1, 5 Days)

DF media 1 +10ng/ml Dkk1, +10ng/ml Noggin, +10ng/ml Igf1, +10ng/ml bFGF (D5)

10 Days → D10

10 Days → D20

D15 → D21

DF media 2 +10ng/ml Dkk1, +10ng/ml Noggin, +10ng/ml Igf1, +10ng/ml bFGF, 10mM DAPT

Photoreceptor production

D30 → D150

DF media 3 +10ng/ml Dkk1, +10ng/ml Noggin, +10ng/ml Igf1, +10ng/ml bFGF, +2ng/ml aFGF

45 days

70 days
Multi-layer Eyecup-like Structure

400 µm
Multi-layer Eyecup-like Structure

Image description:
- Neurosensory Retina
- RPE

Scale bar: 400 µm
Multi-layer Eyecup-like Structure

400 µm
Polycaprolactone (PCL)
Cost?

Less than $50,000 (including ten years of follow up).
Imagine It!

- Gene therapies for all patients with early retinal disease.
- Stem cell based photoreceptor transplants for all patients with late stage photoreceptor disease.
How big are these goals?
Population Survey

• 1000 consecutive families with Mendelian retinal disease
Population Survey

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- Causative mutations were found in 76% overall ($980 per family)
Population Survey

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• 104 different disease-causing genes in these 1000 families
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• 10 Usher genes
Stone Clinic Population Survey

Usher Patients 7.4%

Usher Genes 10.1%

<table>
<thead>
<tr>
<th>Gene</th>
<th>Rank</th>
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<tr>
<td>USH2A</td>
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<tr>
<td>USH1F</td>
<td></td>
</tr>
<tr>
<td>MYO7A</td>
<td></td>
</tr>
<tr>
<td>CDH23</td>
<td></td>
</tr>
<tr>
<td>GPR98</td>
<td></td>
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<td>USH1C</td>
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<td>USH1G</td>
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<td>USH3A</td>
<td></td>
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</table>

Gene	Rank
Pa3ents	per	Gene

Stone Clinic Population Survey
Usher Patients 7.4%
Usher Genes 10.1%
Three Perspectives

Money

Science  Treatment
Three Perspectives

Science

Treatment

Money
Three Perspectives

Treatment

Money

Science
Post Traumatic Stress Disorder

- You, a family member or close friend are suddenly and seriously injured
Post Traumatic Stress Disorder

• You, a family member or close friend are suddenly and seriously injured

• Anxiety, depression, poor sleep, uncontrollable thoughts
Post Traumatic Stress Disorder

- You, a family member or close friend are suddenly and seriously injured
- Anxiety, depression, poor sleep, uncontrollable thoughts
- Triggers (emails, phone calls, news stories, clinic visits, test results)
Post Traumatic Stress Disorder

- You, a family member or close friend are suddenly and seriously injured
- Anxiety, depression, poor sleep, uncontrollable thoughts
- Triggers (emails, phone calls, news stories, clinic visits, test results)
- Caregivers are also susceptible (compassion fatigue)
Three Recent Loud Noises
(none proved to be substantive)

• RIKEN suspends clinical trial
• Immunity to viruses may preclude eligibility for a trial
• CRISPR causes mutations
RIKEN suspends first clinical trial involving induced pluripotent stem cells

Ken Garber

Published online 08 September 2015

The human eye retina is formed from numerous layers, with the retinal pigment epithelium forming a layer on top.
Altered virus could help more patients to become eligible for human gene therapy trials

June 13, 2017
CRISPR Gene-Editing Can Cause Hundreds of Unexpected Mutations

Uh oh...
BEC CREW  30 MAY 2017

It's been hailed as one of the most potentially transformative inventions in modern medicine, bringing the prospect of designer babies closer than any other technology to date, but CRISPR-Cas9 could be riskier than we thought.

The technology that could spark a gene-editing revolution has been caught introducing hundreds of unintended mutations into the genome, and with scientists already testing it in humans, it's set off some serious alarm bells.
This story had an immediate effect on stock prices.

- Editas Medicine (NASDAQ:EDIT) ↓ 15.7%
- CRISPR Therapeutics (NASDAQ:CRSP) ↓ 6.9%
- Intellia Therapeutics (NASDAQ:NTLA) ↓ 14.9%
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Millions of dollars changed hands because of three mice.
Reaction was swift and negative.

- This is a terrible paper and as a reviewer I would have dismissed it from the first round of review.
- I found stunning this paper got so widely promoted on such unsubstantiated claims, all based on the media release piece only.

-- Gaetan Burgio, JCSMR
But, what if . . . ?
But, what if . . . ?

We will fix it.
A Problem You Didn’t Hear About
A Problem You Didn’t Hear About

F 24hrs

H 10 days
A Problem You Didn’t Hear About

24hrs

10 days

10 days

10 days
A Problem You Didn’t Hear About

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>FibroGRO™</th>
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<tbody>
<tr>
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<td>Male</td>
<td>++</td>
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<tr>
<td>T2</td>
<td>36</td>
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<td>T6</td>
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<td>Female</td>
<td>-</td>
</tr>
<tr>
<td>T5</td>
<td>81</td>
<td>Male</td>
<td>-</td>
</tr>
</tbody>
</table>
A Problem You Didn’t Hear About

24hrs

74 years old

10 Days

81 years old
Our Path to the Cures
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• Work primarily within a nonprofit, philanthropic culture.
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• Share ideas freely; publish quickly, share detailed methodology when asked.
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• Work primarily within a nonprofit, philanthropic culture.

• Share ideas freely; publish quickly, share detailed methodology when asked.

• Leave no one behind; work on lots of different diseases (early and late stages) and lots of different genes at the same time.
Our Path to the Cures

• Reduce waste; avoid detailed annual reports, institutional overhead, and unnecessary administrative layers.
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• Confine discussions of progress and plans to published papers, formal scientific presentations.
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• Confine discussions of progress and plans to published papers, formal scientific presentations.

• Replace animal models with cultured cells whenever possible; use cells for efficacy, animals for safety.
Our Path to the Cures

• Reduce the cost and improve the sensitivity of genetic tests, so that one can find patients who might wish to join trials and, find the remaining disease-causing genes.
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• Develop philanthropically funded GMP facilities to reduce the costs of therapeutic vectors and cells.
Our Path to the Cures

• Develop reusable gene therapy strategies, especially genome editing methods for large and/or expression-sensitive genes.
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• Develop cell therapies based upon patient-derived stem cells, to reduce the risk of immune rejection.
Our Path to the Cures

- Develop reusable gene therapy strategies, especially genome editing methods for large and/or expression-sensitive genes.
- Develop cell therapies based upon patient-derived stem cells, to reduce the risk of immune rejection.
- Analyze existing clinical data to determine the best timing and anatomic location for therapy.
Usher Cohort
2207 patients, 1765 families

- William Kimberling
- Sam Jacobson
- Jerry Fishman
- Richard Weleber
- Elias Traboulsi
- Elise Heon
- Byron Lam

- Claes Moller
- Sten Andreasson
- Alex Levin
- Christine Kay
- Raymond Iezzi
- Mina Chung
- Alessandro Iannaccone
Usher Cohort
2207 patients, 1765 families

- USH2A 609
- MYO7A (1B) 249
- CDH23 (1D) 68
- USH3A 43
- PCDH15 (1F) 28
- USH1C 30
- GPR98 (2C) 10
- USH1G 1
Goldmann Perimetry
Usher Syndrome Natural History Study

Todd Scheetz
Adam DeLuca
Nicole Tatro

1989
Our Path to the Cures

• Focus almost entirely on Phase I-II clinical trials with long but fairly conventional follow-up.
Our Path to the Cures

• Focus almost entirely on Phase I-II clinical trials with long but fairly conventional follow-up.

• View every aspect of our work from the perspective of the clinical outcomes we want (and the realities of the diseases we are facing) instead of the perspectives of financial benefit, customary practice, or personal convenience.
Our Path to the Cures

- Do everything with a sense of URGENCY.
Summary

• Positive thinking (realistic hope)
• Leave no one behind
• Genetic testing – < $1000
• Gene therapy – < $20,000
• Stem cell therapy – < $50,000
Acknowledgements