Improvements in Visual Function following Electroacupuncture & other Promising Treatments for Retinitis Pigmentosa

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Disclosures

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Impact of Potential Vision Loss from RP
Introduction to Vision Loss in RP

- Roughly 1 in 5 patients diagnosed before age 18
- Age of onset of RP varies for different genetic mutations, but across all patients, average age of diagnosis = 35 years
- Previous survey: 23% of RP patients were not aware that they had visual field loss, although they showed visual field constriction

- Central vision and visual acuity (VA) is typically not lost until late in the disease in typical cases
- ~50% have VA better than 20/40
- X-linked have worst VA (~5-15% of patients) & autosomal dominant have best VA (~50-60% of patients)
- Only 0.5% over age 45 had no light perception OU
Retinitis Pigmentosa (RP) is caused by genetic defects resulting in the dysfunction, degeneration and/or maldevelopment of photoreceptors or the RPE. Potential therapies are directed to these components.
What treatments are on the Horizon for RP?

The horizon leans forward, offering you space to place new steps of change.

- Maya Angelo
Basic Science: TUDCA

- Tauroursodeoxycholic acid (TUDCA) is an endoplasmic reticulum (ER) chemical chaperone; component of bear bile acid.
- TUDCA is effective in alleviating ER stress & preventing apoptosis in many disease models.
- Rapid cone degeneration in LCA caused by ER stress induced by S-opsin aggregation.
- Efficacy for preventing retinal degeneration in mouse/rat models.
- In \textit{Lrat}^{-/-} mice treated with TUDCA, ~3-fold increase in cone density in the ventral & central retina as compared with vehicle treated mice.
Basic Science: TUDCA

• Boatright, Pardue et al.:
  • TUDCA-treated rd10 mouse retinas had 5-fold more photoreceptors than vehicle-treated retinas
  • Light- & Dark-adapted ERG responses were 2-fold greater in rd10 mice treated with TUDCA than w/ vehicle
  • Group from Spain: 3-fold more photoreceptors & greater ERG responses in P23H rats tx’ed w/ TUDCA

• Univ. of Iowa: TUDCA preserved ERG b-waves & ONL in rd10 mice, but was not successful in more rapidly progressive disease models (rd1 & rd16)
Time for Translation: TUDCA

- Human trials not yet underway, but planned by FFB
- TUDCA may be a good candidate in treating RP & LCA
  - not light sensitive & effective under normal light-dark cycle
  - can be delivered to the eye by oral intake
  - already approved for treating various liver & gallbladder diseases
  - may intervene at young ages when gene therapy might be too traumatic to the developing eye
  - may maximize the preservation of cones at older ages
Acupuncture for RP

- RP patients motivated to try CAM since limited tx options
- In 2006-07, survey of complementary therapy usage in 96 RP patients: 42% had tried acupuncture, of which, 61% indicated a subjective improvement in vision

Evidence to support the hypothesis that acupuncture may improve vision in RP
- fMRI demonstrated physiological changes in the eye and/or brain in response to stimulation of vision-related acupoints in normally sighted patients
- Increased retinal thickness & neurotrophic factors in rats with RP-like degeneration
Acupuncture for RP

- 2 published case series indicating VA &/or VF improvements in RP patients tx’ed with acupuncture
  - no RCTs or studies of mechanisms in RP

- Initiated pilot study using Dr. Andy Rosenfarb’s protocol based on his experience >15 years tx 400+ RP patients
  - 12 RP subjects treated by JHU acupuncturist
    - 10 half-hour sessions over 2 weeks
    - pre- and post-tx vision testing at Wilmer
Acupuncture for RP

- Dark Adapted Full-field Sensitivity Test (FST)
- White light flashed in ERG ganzfeld
- 45 mins. dark-adaptation

- 3 of 9 subjects had a significant 10.3-17.5dB (i.e. 13-53 fold) FST improvement in both eyes at 1 week post-tx maintained for at least 4-6 mos
  - well outside typical test-retest variability (95% CI: 3-3.5dB) in RP
Acupuncture for RP

- SST-1 Dark Adaptometry (rate or time course)
  - Dark-adaptation shortened in both subjects tested on average by 48.5% at 1 wk. (range 36-62% across 10-30dB)
    - outside typical coefficients of variation <30% previously determined in RP and normals

- One subject had 0.2 logMAR VA improvement
- Another had 0.55 logCS contrast sens. improvement
- Another subject developed >20% improvement in Goldmann visual field retinal area in both eyes at 1-3 mos post-tx
Acupuncture for RP

- Subjective Improvements

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<th>vision at night in dark (scotopic)</th>
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Acupuncture for RP

- CME reduction on SD-OCT in both subjects with CME pre-tx
Acupuncture Mechanisms

• Electroacupuncture increases blood fluidity by decreasing platelet aggregation in the systemic vascular system

• Ocular blood flow (OBF) in the retrobulbar arteries with color Doppler imaging (CDI) measured in the last 2 subjects

• Changes in vascular resistance index and velocity profiles in both RP subjects suggest a moderate but significant OBF increase in the central retinal artery at 1-2 weeks post-tx
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Next Steps:

• Obtain funding to continue to explore changes in OBF as a potential mechanism to help explain improvements in vision

• Explore factors to help predict which RP patients respond
Clinical Trials

CNTF: Ciliary Neurotrophic Factor in RP

- Neurotech: Encapsulated Cell Technology
- NT-501 implants produced CNTF consistently over 2 year period; favorable pharmacokinetics
Clinical Trials

CNTF: Ciliary Neurotrophic Factor in RP

- Neurotech: Encapsulated Cell Technology
- NT-501 implants produced CNTF consistently over 2 year period; favorable pharmacokinetics
- Cone density preserved in implanted eye of 3 subjects monitored with AO-SLO
Two paths to ameliorate the biochemical blockade

Gene augmentation with wildtype RPE65

**Gene therapy restores vision in a canine model of childhood blindness**

Gregory M. Acland¹, Gustavo D. Aguirre¹, Jharna Ray¹, Qi Zhang¹, Tomas S. Aleman², Artur V. Cideciyan², Susan E. Pearce-Kelly¹, Vibha Anand², Yong Zeng², Albert M. Maguire², Samuel G. Jacobson², William W. Hauswirth² & Joan Bennett²

*nature genetics • volume 28 • may 2001*

**Gene Therapy for Leber Congenital Amaurosis Caused by RPE65 Mutations**

Safety and Efficacy in 15 Children and Adults Followed Up to 3 Years

Samuel G. Jacobson, MD, PhD; Arian V. Cideciyan, PhD; Ramakrishna Rattanarun, MD, Elise Heon, MD; Sharon B. Schwartz, MS, CCC; Alejandro J. Roman, MS; Marc C. Pedersen, MD; Tomas S. Alemán, MD; Sanford L. Boyce, MS; Alexander Sumaroka, PhD, Thomas J. Conlon, PhD; Roberto Calcedo, PhD; Ji-Jing Pang, MD, PhD; Kirsten E. Erger, BS; Melani B. Olivares, BA; Cristina L. Mullins, BA; Małgorzata Swider, PhD; Shalesh Kauhal, MD, PhD; William J. Feuer, MS; Alessandro Bannaccone, MD, MS; Gerald A. Fishman, MD; Edwin M. Stone, MD, PhD; Barry J. Byrne, MD, PhD; William W. Hauswirth, PhD

Two paths to ameliorate the biochemical blockade

- Bypass with 9-cis-retinoid chromophore
- Gene augmentation with wildtype RPE65

**Clinical Trials**

**Rapid restoration of visual pigment and function with oral retinoid in a mouse model of childhood blindness**

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Synthetic Drug therapy: 11-cis-retinal replacement

Mutation defect blocks recycling of chromophore needed for vision

Pharmacologic Bypass here
GVF Animation: JHU RP Subject Screening
Remaining Questions

- What is the best outcome measure for this treatment & disease?
  - Goldmann Visual Field area vs. static threshold sensitivity or combo?
  - Validate Octopus 900 kinetic VFs as reliable successor to Goldmann
Remaining Questions

- Differing individual responses?
- What is appropriate dosing regimen?
- What happens to disease progression?

**Scenario 0:** No treatment given; retinal degeneration & VF loss continue unchecked.

**Scenario 1:** Treatment improves VF by 30%, but degeneration unchecked.

**Scenario 2:** Re-treatments every 2 years; degeneration unchecked.

**Scenario 3:** Continued treatments slow degeneration by 50%.

**Scenario 4:** Continued treatments halt degeneration.

 Premise: The patient has normal VF's until age 22, & starts losing fields until diagnosed at age 30.
Future Directions
In the Meantime…

- ODs can play an important role in referring RP patients as potential study participants
  - Acupuncture study
  - Genetic screening (NIH EyeGENE program) to help identify future trial participants
Nutritional supplements

Clinical Trial of Lutein in Patients With Retinitis Pigmentosa Receiving Vitamin A

How Strong Is the Evidence That Nutritional Supplements Slow the Progression of Retinitis Pigmentosa?

Letter From the DSMC Regarding a Clinical Trial of Lutein in Patients With Retinitis Pigmentosa

We, the members of the Data Safety Monitoring Committee (DSMC) for Berson and colleague’s clinical trial of lutein in patients with retinitis pigmentosa who are receiving vitamin A, share many of the concerns Massof and Fishman expressed in their editorial.

We have carefully evaluated the data from the trial and view that the authors’ conclusion and the section on “Application to Clinical Practice” overstate the strength of evidence for the use of lutein.
Nutritional supplements

- For your RP patients on 15,000 IU Vit. A palmitate:
  - Potential for liver toxicity
  - Refer to general physician to obtain a liver function profile to test for possible elevated concentrations of liver enzymes, such as:
    - aspartate transaminase (AST)
    - alanine transaminase (ALT)
    - alkaline phosphatase
  - Obtain liver panel 6 months after starting Vit. A then annually
Argus II Retinal Prosthesis

- Developed by Second Sight Medical Products
- Very recent FDA approval following multicenter, international clinical trial with 30 subjects (5 at JHU Wilmer)
Argus II Retinal Prosthesis

- Epi-retinal implantation (6x10 array)
- Creates artificial vision in patients with bare light perception
- May be most helpful for orientation & mobility, detect movement, high contrast objects
- Realistic patient expectations (can’t read or recognize faces)