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

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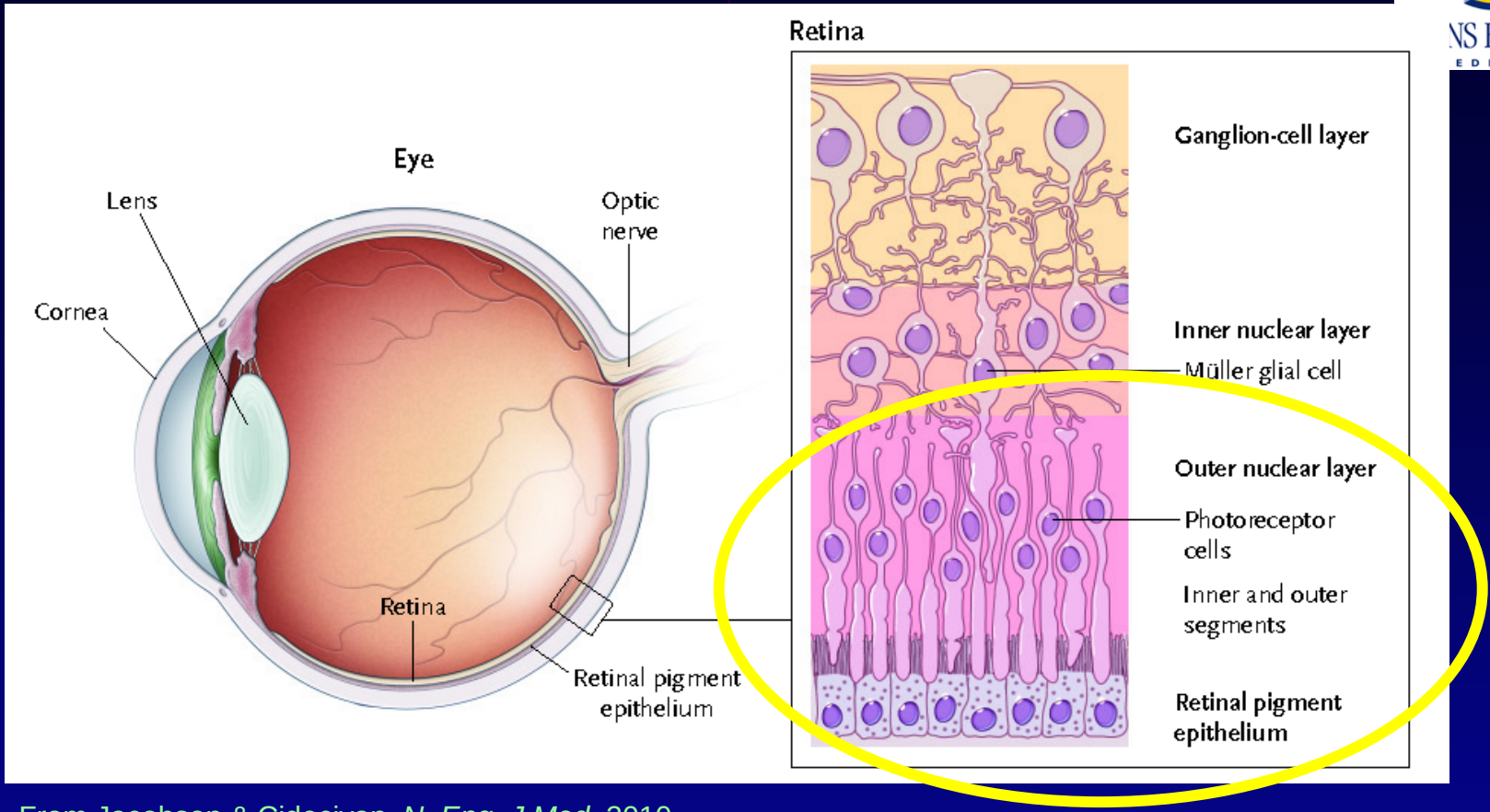
Disclosures

- Dr. Bittner is a paid consultant for QLT Inc.
- Dr. Bittner is supported by NIH/NEI K23EY018356 “Training in Clinical Trials for Low Vision”

Impact of Potential Vision Loss from RP

Introduction to Vision Loss in RP

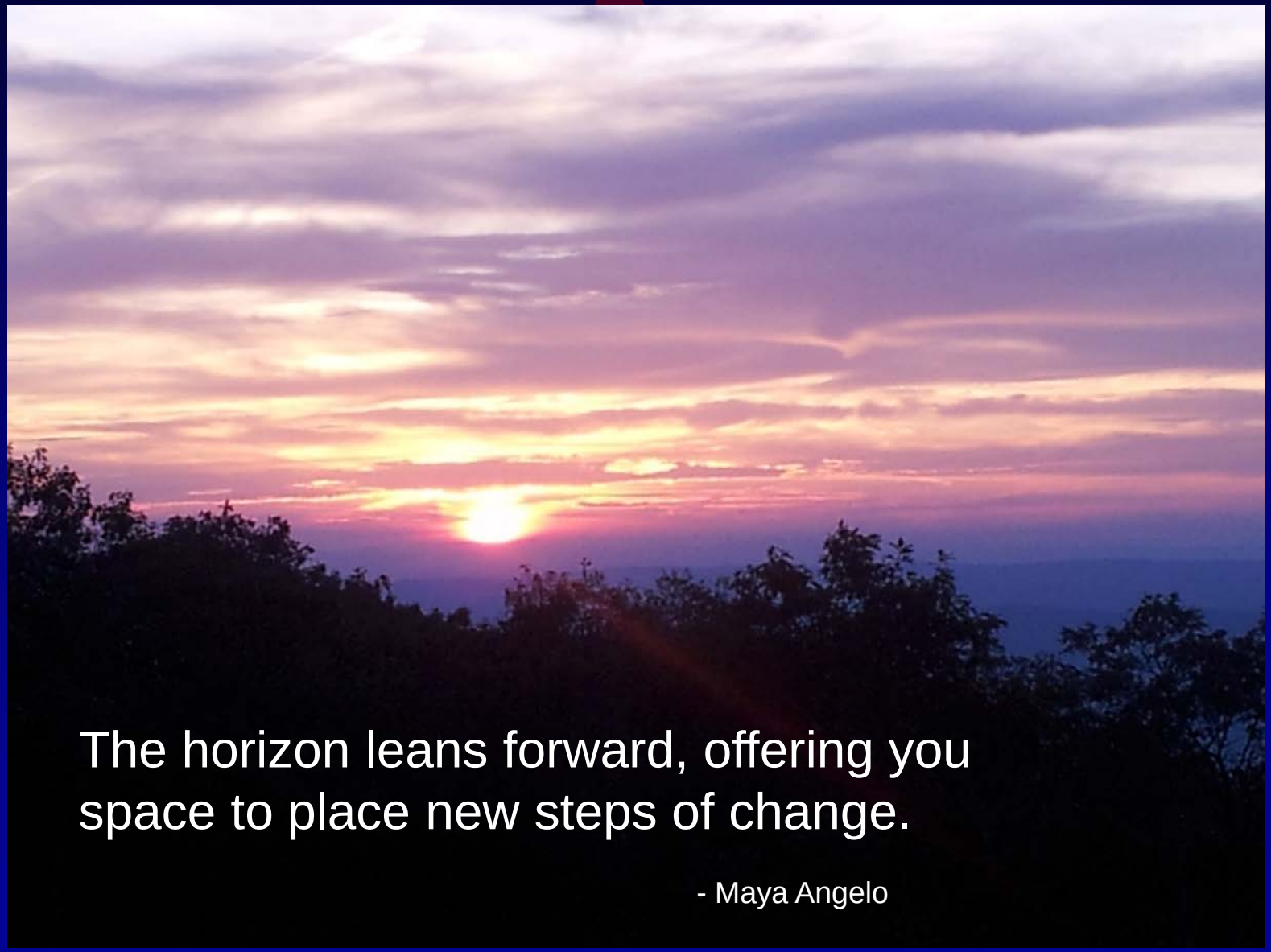
- Roughly 1 in 5 patients diagnosed before age 18
- Age of onset of RP varies for different genetic mutations, but across all patients, average age of diagnosis = 35 years
- Previous survey: 23% of RP patients were not aware that they had visual field loss, although they showed visual field constriction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

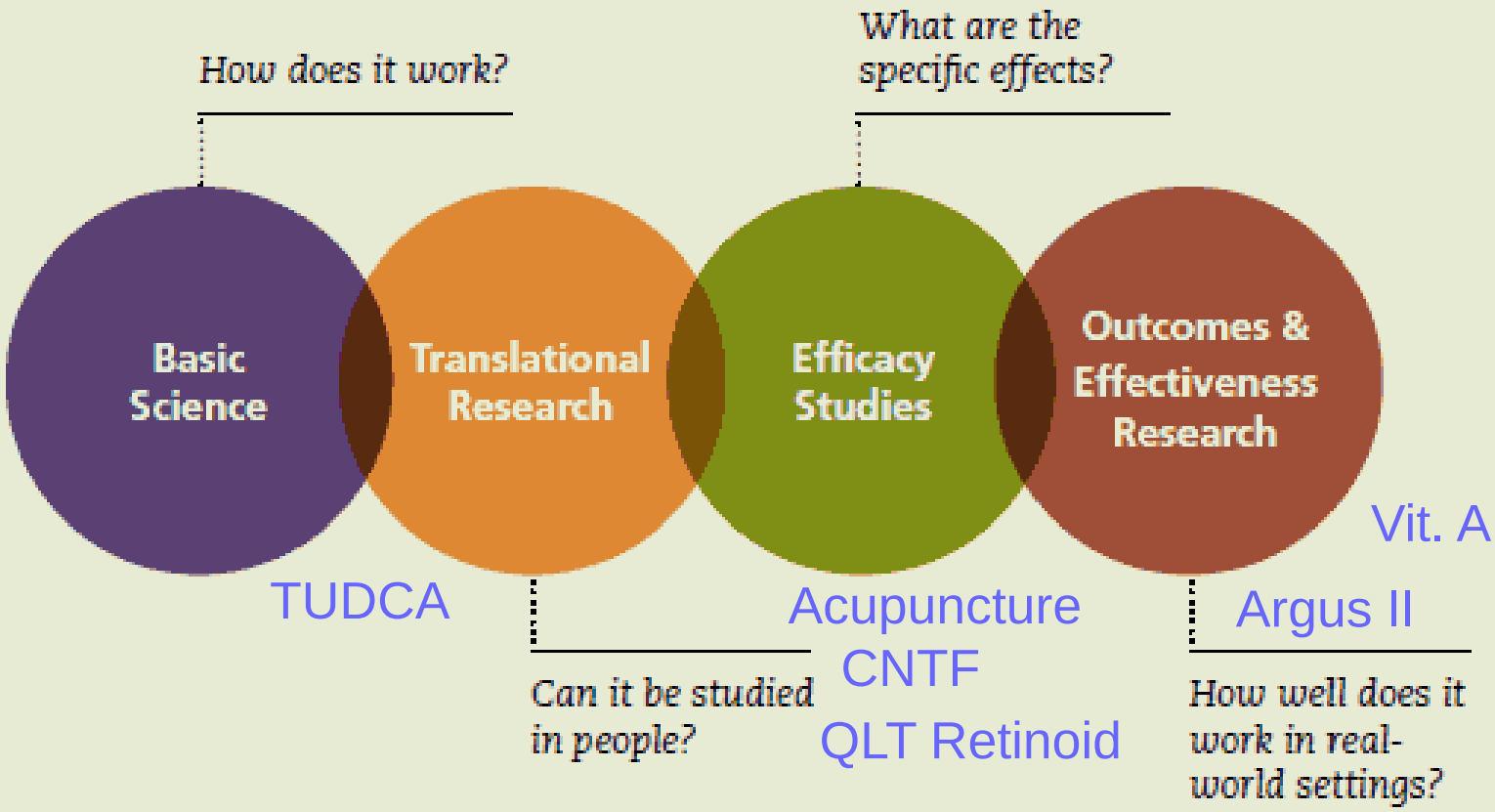


From Jacobson & Cideciyan, *N. Eng. J Med.* 2010

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.

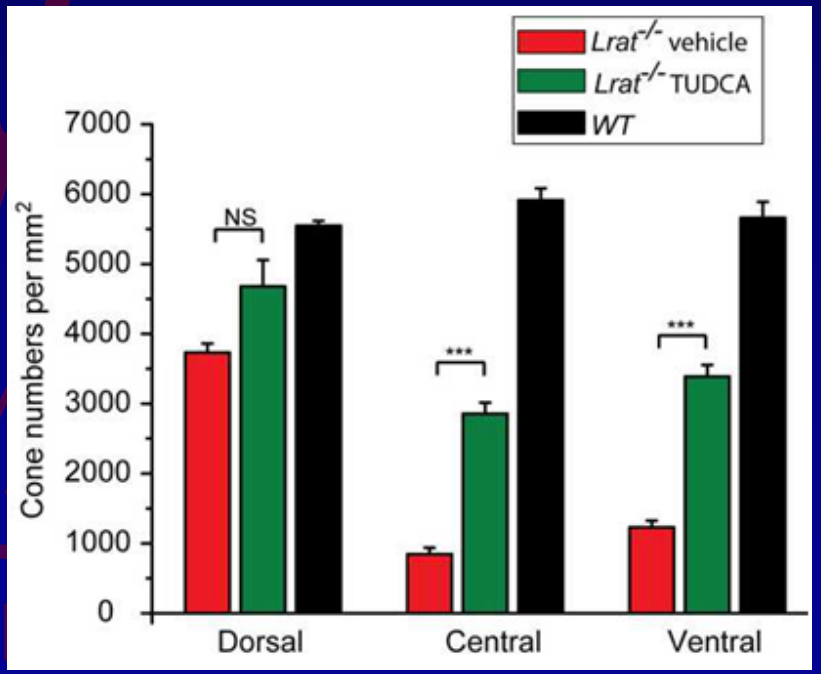
What treatments are on the Horizon for RP?




How does it work?
What are the specific effects?
Basic Science
Translational Research
Efficacy Studies
Outcomes & Effectiveness Research
TUDCA
Vit. A
Acupuncture
CNTF
QLT Retinoid
Argus II
Can it be studied in people?
How well does it work in real-world settings?

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 *Lrat*$^{-/-}$ mice treated w/ TUDCA , ~3-fold increase in cone density in the ventral & central retina as compared w/ 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

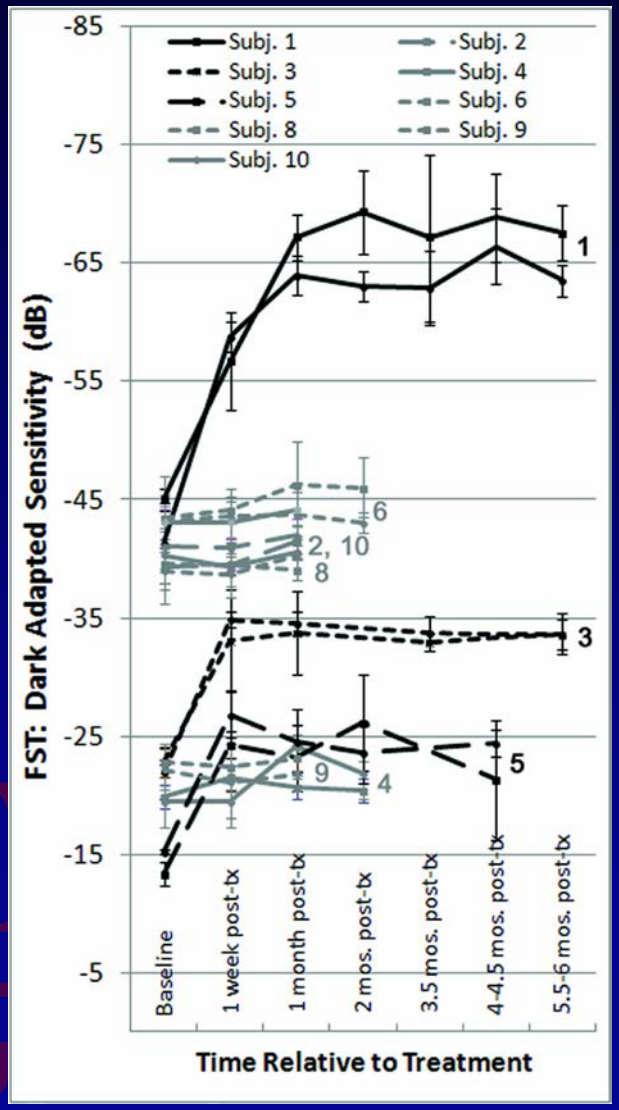
- 2 published case series indicating VA &/or VF improvements in RP patients tx'ed with acupuncture
  - no RCTs or studies of mechanisms in RP

- 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

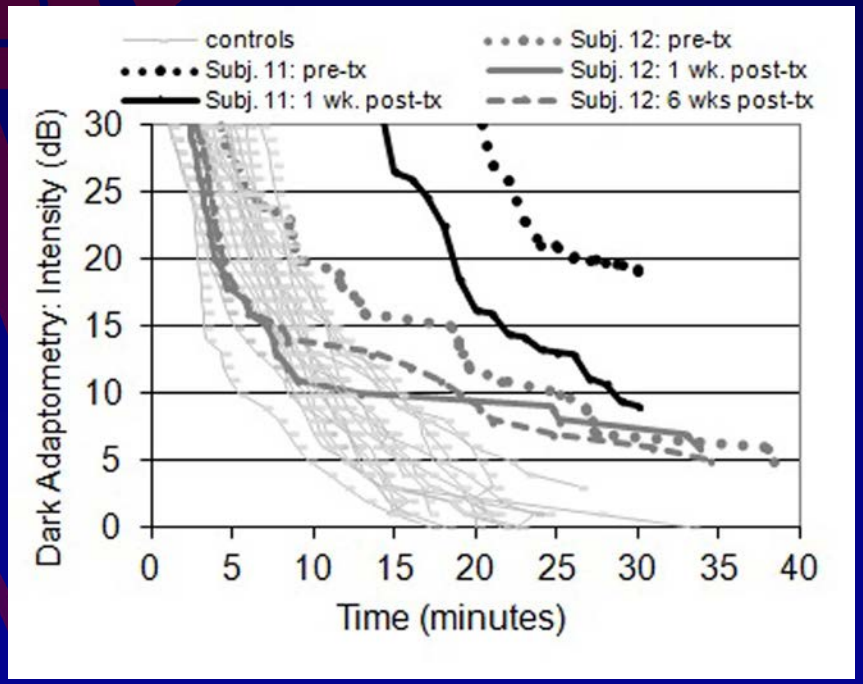
- **Dark Adapted Full-field Sensitivity Test (FST)**
- White light flashed in ERG ganzfeld
- 45 mins. dark-adaptation

- 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

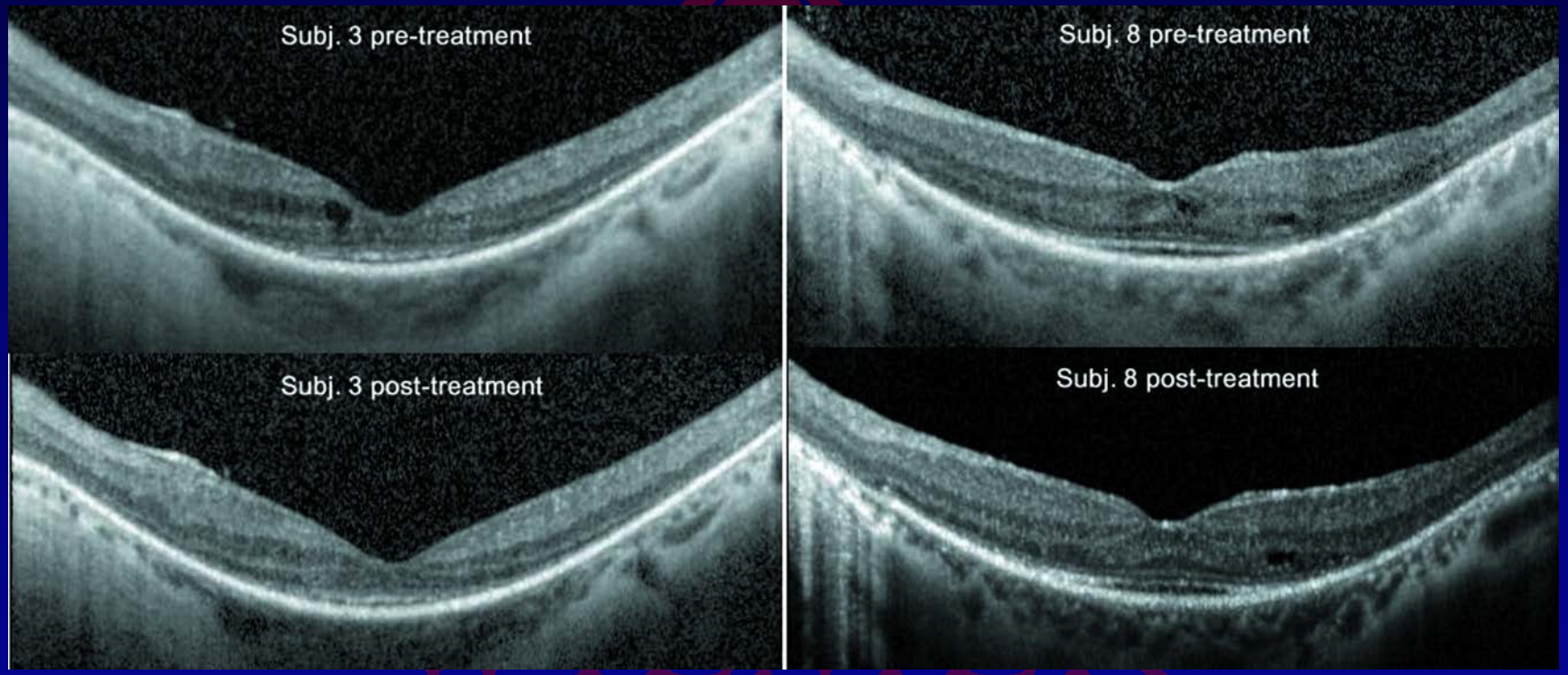
Acupuncture for RP

- Subjective Improvements

ID	glare	distance clarity	near reading or computer	contrast sensitivity	visual field area	visual field clarity/brightness	vision in dim areas/ dusk (mesopic)	color vision	vision at night in dark (scotopic)	bright to dim transition / adaptation	photopsias dec. intensity & area	reduced eye strain/fatigue
1	-	-	-	-	-	-	-	+	+	+	+	-
2	-	-	-	-	-	-	+	+	-	-	-	-
3	-	-	-	+	-	-	-	+	+	+	-	-
4	-	+	+	-	+	+	+	+	-	-	-	-
5	-	-	-	-	-	+	+	-	-	-	+	-
6	-	-	-	+	-	+	+	+	+	+	-	-
7	-	-	-	-	-	-	-	+	+	+	-	-
8	-	-	-	-	+	-	-	-	-	-	-	-
9	-	-	-	-	-	-	-	-	-	-	-	-
10	-	-	-	-	+	-	-	-	-	-	-	+
11	-	+	+	-	-	-	-	+	+	-	+	-
12	-	-	-	-	-	+	-	+	+	+	-	-
total	0	2	2	2	3	4	4	8	6	5	3	1

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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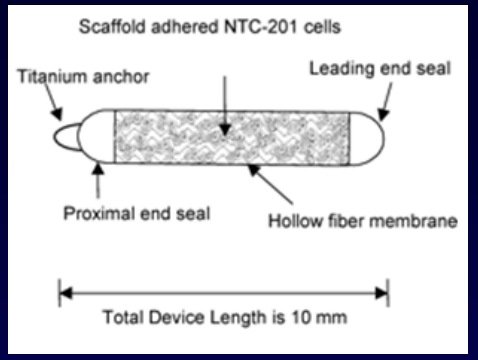
Next Steps:

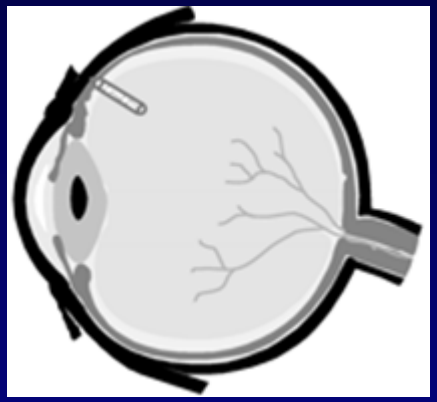
- Obtain funding to continue to explore changes in OBF as a potential mechanism to help explain improvements in vision
- Explore factors to help predict which RP patients respond

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

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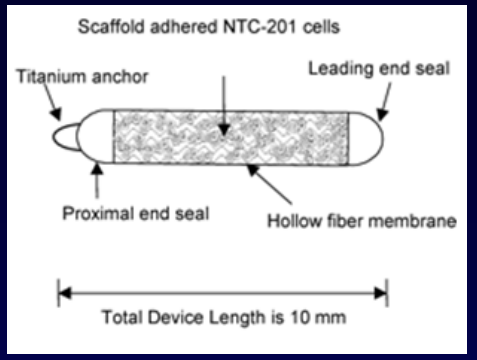
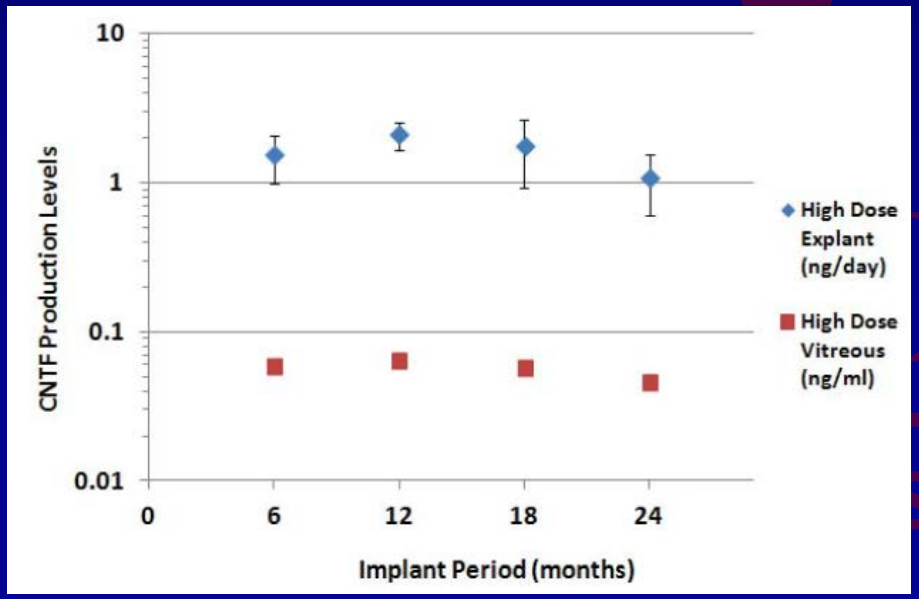
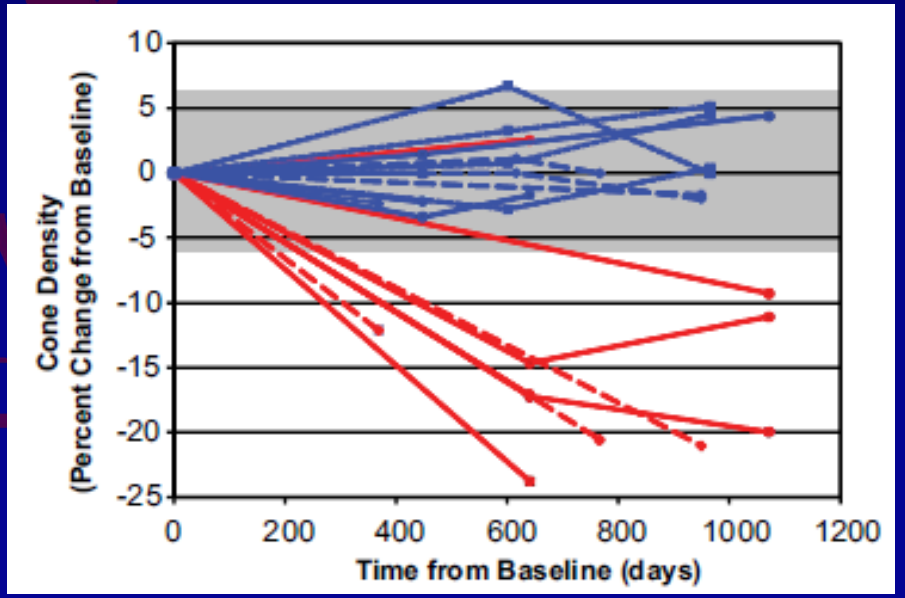


- Neurotech: Encapsulated Cell Technology
- NT-501 implants produced CNTF consistently over 2 year period; favorable pharmacokinetics
- Cone density preserved in implanted eye of 3 subjects monitored with AO-SLO





Clinical Trials

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. Acland[1], Gustavo D. Aguirre[1], Jharna Ray[1], Qi Zhang[1], Tomas S. Aleman[2], Artur V. Cideciyan[2], Susan E. Pearce-Kelling[1], Vibha Anand[2], Yong Zeng[2], Albert M. Maguire[2], Samuel G. Jacobson[2], William W. Hauswirth[3] & Jean Bennett[2]

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; Artur V. Cideciyan, PhD; Ramakrishna Ratnakaram, MD; Elise Heon, MD; Sharon B. Schwartz, MS, CGC; Alejandro J. Roman, MS; Marc C. Peden, MD; Tomas S. Aleman, MD; Sanford L. Boye, 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; Malgorzata Swider, PhD; Shalesh Kaushal, MD, PhD; William J. Feuer, MS; Alessandro Iannaccone, MD, MS; Gerald A. Fishman, MD; Edwin M. Stone, MD, PhD; Barry J. Byrne, MD, PhD; William W. Hauswirth, PhD

Arch Ophthalmol. 2012;130(1):9-24.

Clinical Trials

Two paths to ameliorate the biochemical blockade

Bypass with 9-*cis*-retinoid chromophore

Gene augmentation with wildtype RPE65

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

J. Preston Van Hooser*, Tomas S. Aleman†, Yu-Guang He*, Artur V. Cideciyan†, Vladimir Kuksa*, Steven J. Pittler‡, Edwin M. Stone§, Samuel G. Jacobson†, and Krzysztof Palczewski*¶**

PNAS | July 18, 2000 | vol. 97 | no. 15 | 8623–8628

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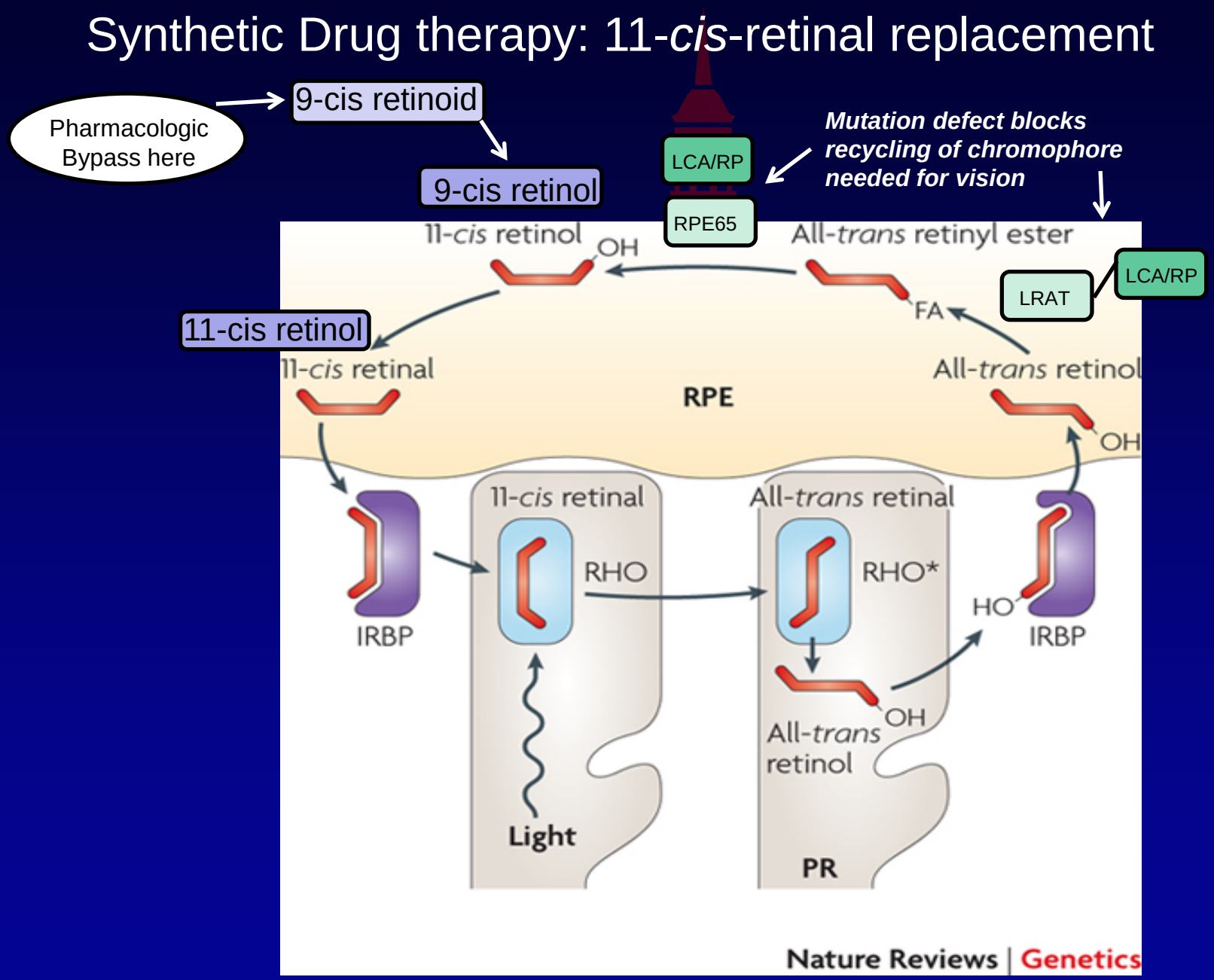
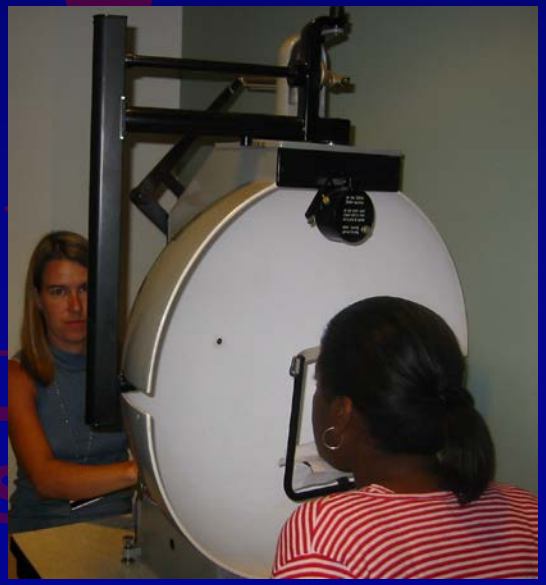
Synthetic Drug therapy: 11-*cis*-retinal replacement



GVF Animation: JHU RP Subject

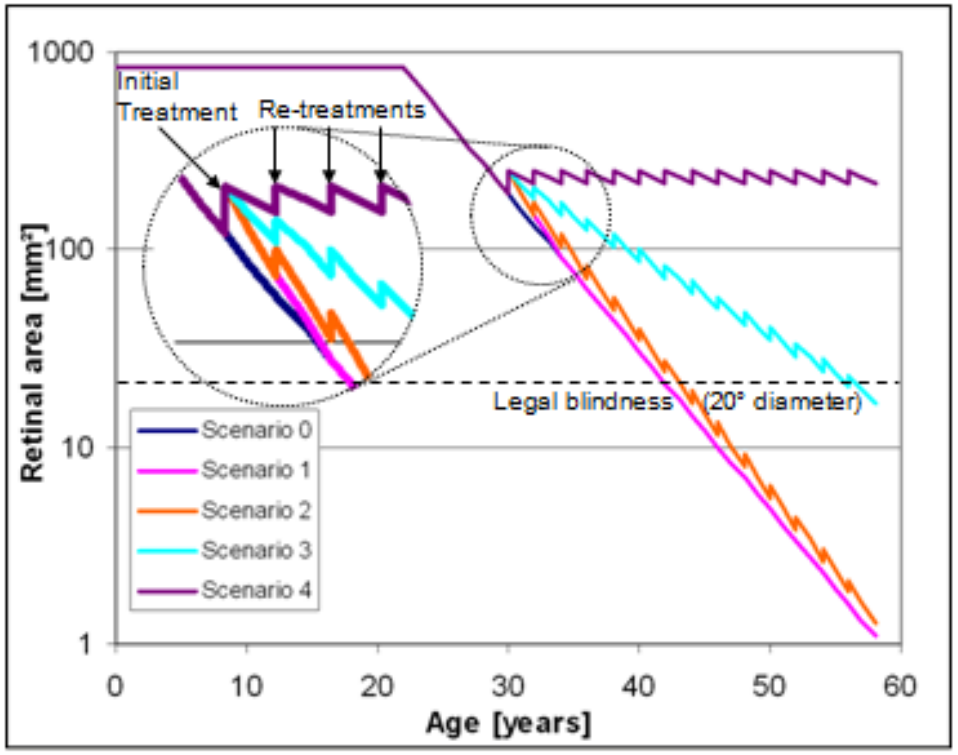
Remaining Questions

- 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?



Premise: The patient has normal VFs until age 22, &starts losing fields until diagnosed at age 30.

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

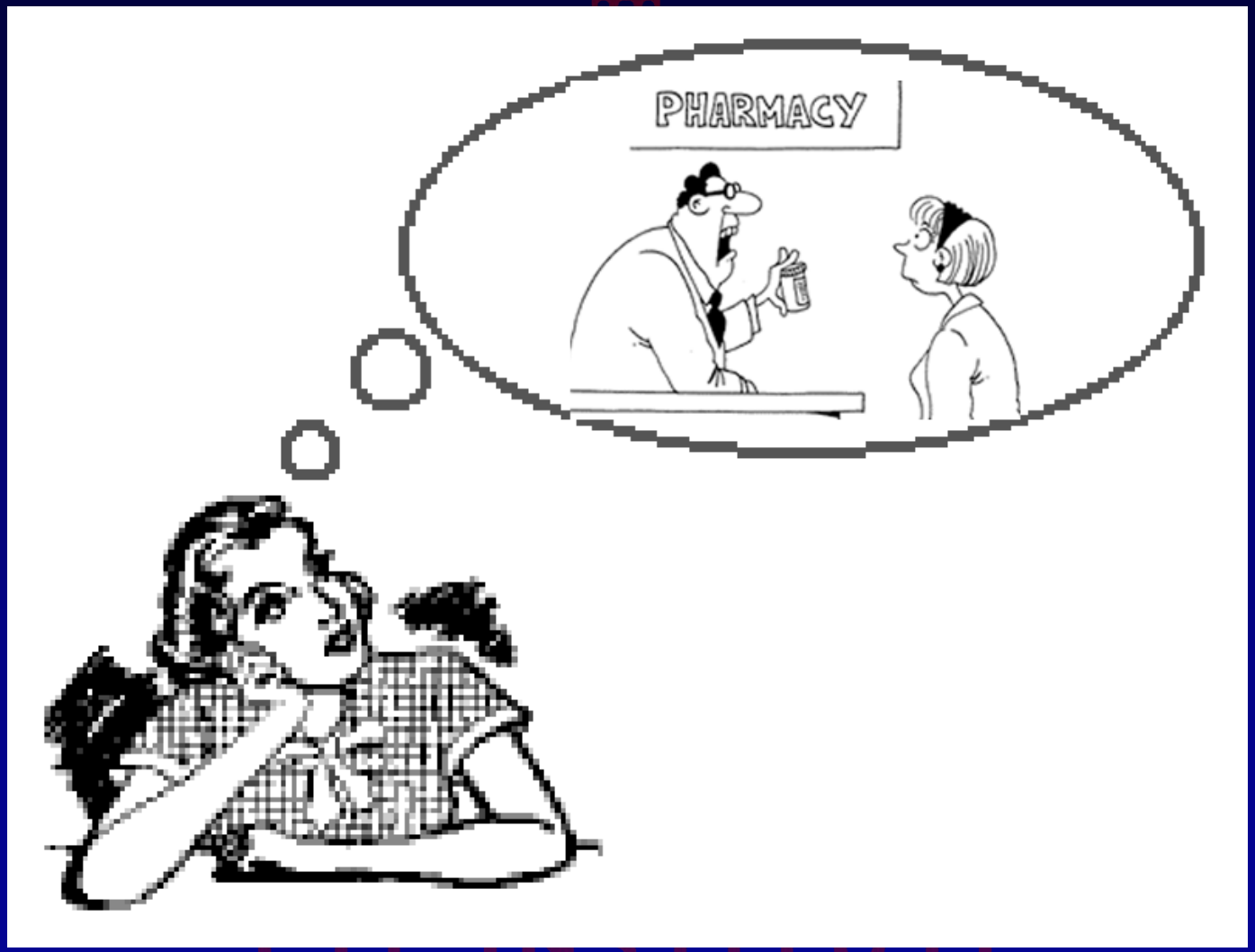
Scenario 1: Treatment improves VF by 30%, but degeneration unchecked

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

Scenario 3: Continued treatments slow degeneration by 50%

Scenario 4: Continued treatments halt degeneration

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

ARCHIVES EXPRESS

Eliot L. Berson, MD; Bernard Rosner, PhD; Michael A. Sandberg, PhD; Carol Weigel-DiFranco, MA; Robert J. Brockhurst, MD; K. C. Hayes, PhD; Elizabeth J. Johnson, PhD; Ellen J. Anderson, RD; Chris A. Johnson, PhD; Alexander R. Gaudio, MD; Walter C. Willett, MD; Ernst J. Schaefer, MD

EDITORIAL

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

ARCHIVES EXPRESS

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,[1] share many of the concerns Massof and Fishman[2] 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)

U.S. Food and Drug Administration

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FDA NEWS RELEASE

For Immediate Release: Feb. 14, 2013
Media Inquiries: Synim Rivers, 301-796-8729, synim.rivers@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA approves first retinal implant for adults with rare genetic eye disease

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)