

Human Gene Transfer Protocol #0910-1005:

**Leber Congenital Amaurosis (LCA) using
Adeno-associated Virus Vector to Deliver the
Gene for Human RPE65 to the Retinal Pigment
Epithelium (RPE) [AAV2-hRPE65v2-301]**

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**RAC
December 1, 2009**



CH08, 9yo

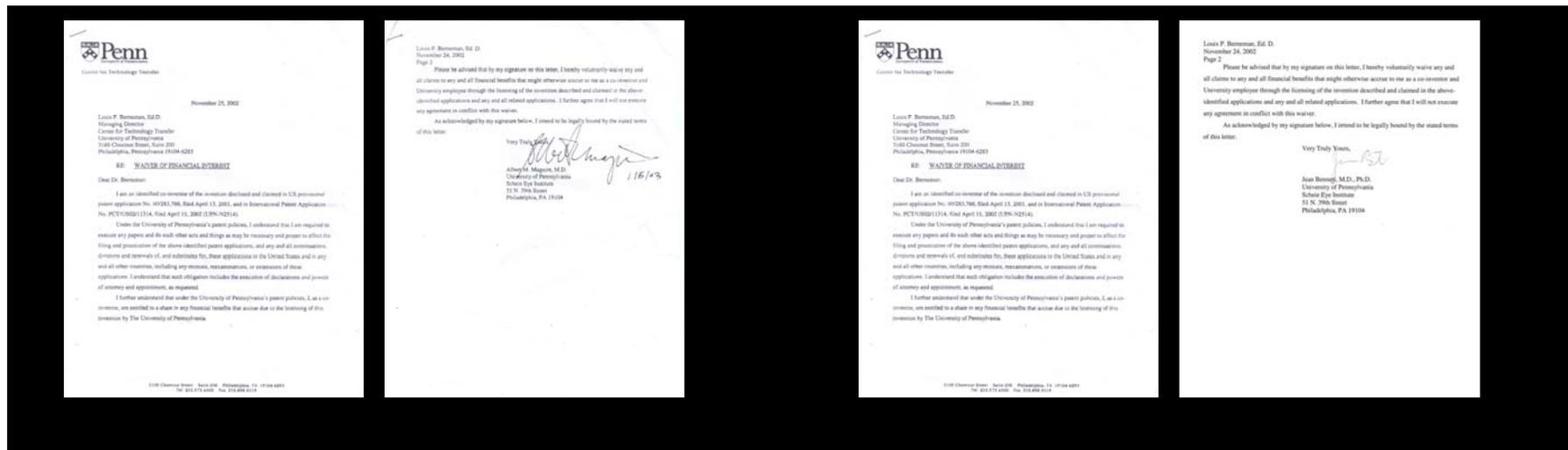
Subjects appearing in this presentation have given media consent and have gone to the media independently

Conflict of Interest Disclosure

Bennett, J, Jacobson, SG, Maguire, AM, Hauswirth, WW, Aguirre, GD, Acland, GD

“Method of treating or retarding the development of blindness, U.S. Patent (Penn Docket #N2514; 2002), pending.

2002: Bennett & Maguire waived any potential financial gain



Outline of Phase 3 LCA-RPE65 Clinical Trial

- Multicenter
- 12 subjects with LCA-RPE65
- Single dose/eye ($1.5E11$ vg) + systemic corticosteroid
- 9 unilateral (contralateral eye as control)
- 3 bilateral (compared to baseline function)
 - For bilateral injections, eye #2 injected <7d post injection of eye #1

Inclusion/Exclusion

- Visual acuity $<20/60$ (WHO criteria) OR
- Visual field defect within 20° of fixation
- Age ≥ 3 yo (vs. 8yo)
- Systemic/ocular factors

Age considerations

- 8yo (Phase I/II)
 - Assent
 - Testing (subjective)
 - Age – degree of improvement
- 3yo (Phase III)
 - Parental consent
 - Testing (objective)
 - Risk/benefit ratio

Dose selection

- Dose = volume X concentration
- Volume – area/number of cells exposed
- MED – principles of clinical research involving vulnerable (pediatric) populations:
 - 45 CFR 46.405 – Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects
- MTD – toxicity is irreversible (CNS)

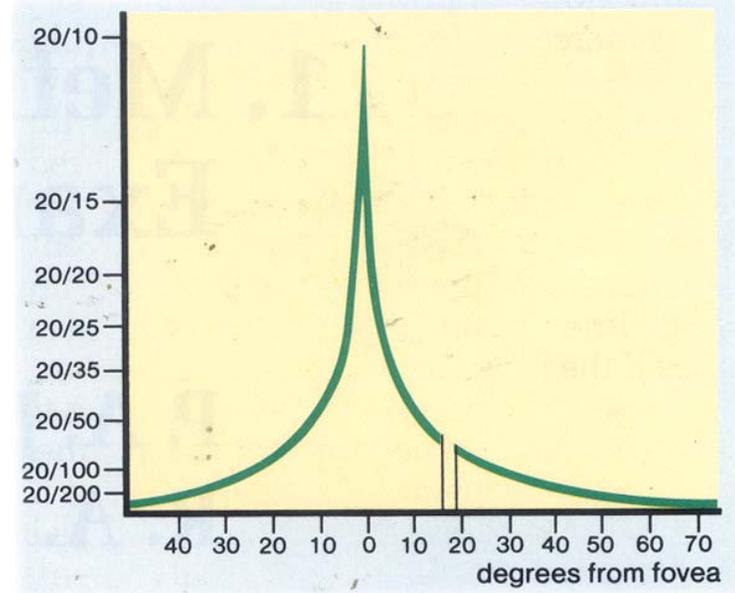
Outcome measures - requirements

- Clinically meaningful (incl. surrogate)
- Applicable to children
- Statistically robust
 - Signal/noise ratio
 - Subjective vs. objective

Subjective measures

- Visual acuity (central)
- Visual field (peripheral)
- Dark adaptometry (sensitivity)
- Placebo/learning/
cognitive effects

Visual Acuity



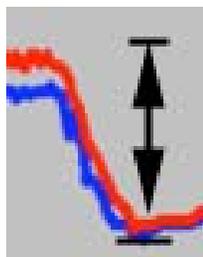
From DJ Spalnton et al, Atlas of Clinical Ophthalmology, JB Lippincott Co, Philadelphia, 1984

Objective measures

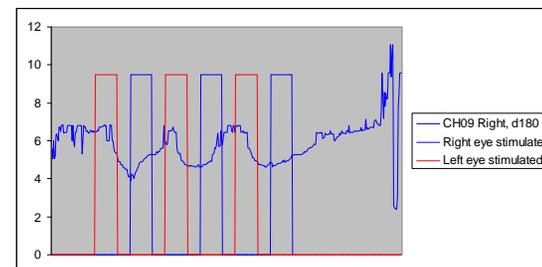
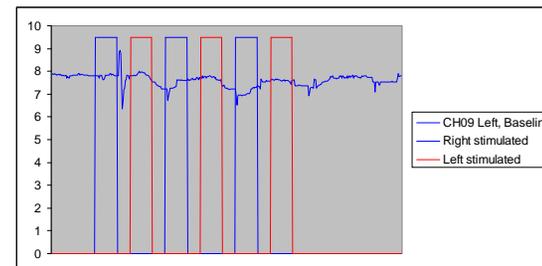
- ERG
- PLR (Marcus-Gunn pupil)
 - Physiologic response to visual stimulus
 - Sensitive (signal/noise)
 - Rapid, non-invasive/age appropriate
 - Correlation to VF

- Ellis 1979, J Neurol Neurosurg Psychiatry 42:1008
- Volpe et al 2009 Curr Eye Res 34:606

PLRs of 8yo
Velocity



Amp



Baseline

40,000X
less light

Day 180

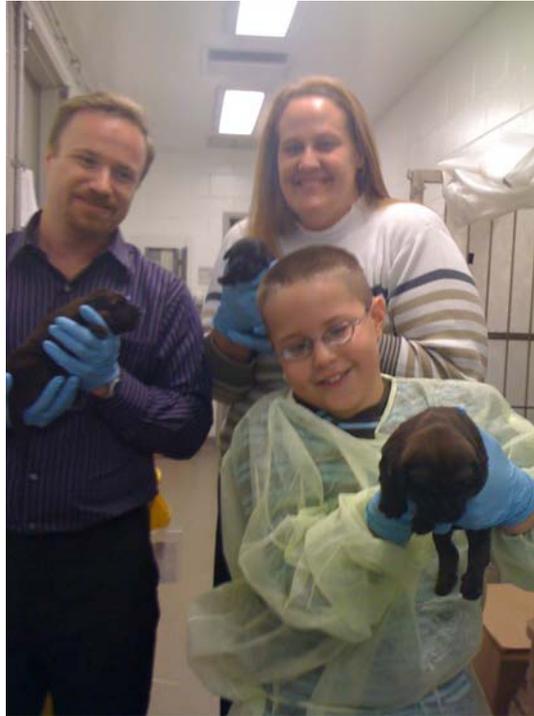
Statistics – Orphan Disease

- Subretinal administration will result in $\geq 20\%$ increase in pupil constriction amplitude and/or velocity in $>80\%$ of injected subjects
 - Well recognized clinical parameter
- Historical probably of success without treatment $<5\%$
- Hypothesized probability of success with treatment $>80\%$
- Power of study $\gggg 99\%$ with a sample size of 12 subjects and a one-sided Type 1 error rate of 0.025
- If probability of success with treatment is only 50%, the power is still 98% to show a benefit of treatment over no treatment

Systemic corticosteroids

- Commonly used in vitreoretinal (pediatric) surgery
- Maximum dose 40 mg/day
- No sign of inflammation (humans)
- AE's minor
- Limited course/rapid taper

Response to questions?



We are grateful for support from:

- Center for Cellular and Molecular Therapeutics at The Children's Hospital of Philadelphia
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- Scheie Eye Institute
- Research to Prevent Blindness
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- Paul and Evanina Mackall Foundation Trust
- Italian Telethon Foundation
- National Center for Research Resources
- Howard Hughes Medical Institute.



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