Leading Regenerative Medicine

CIRM Presentation – May 2012

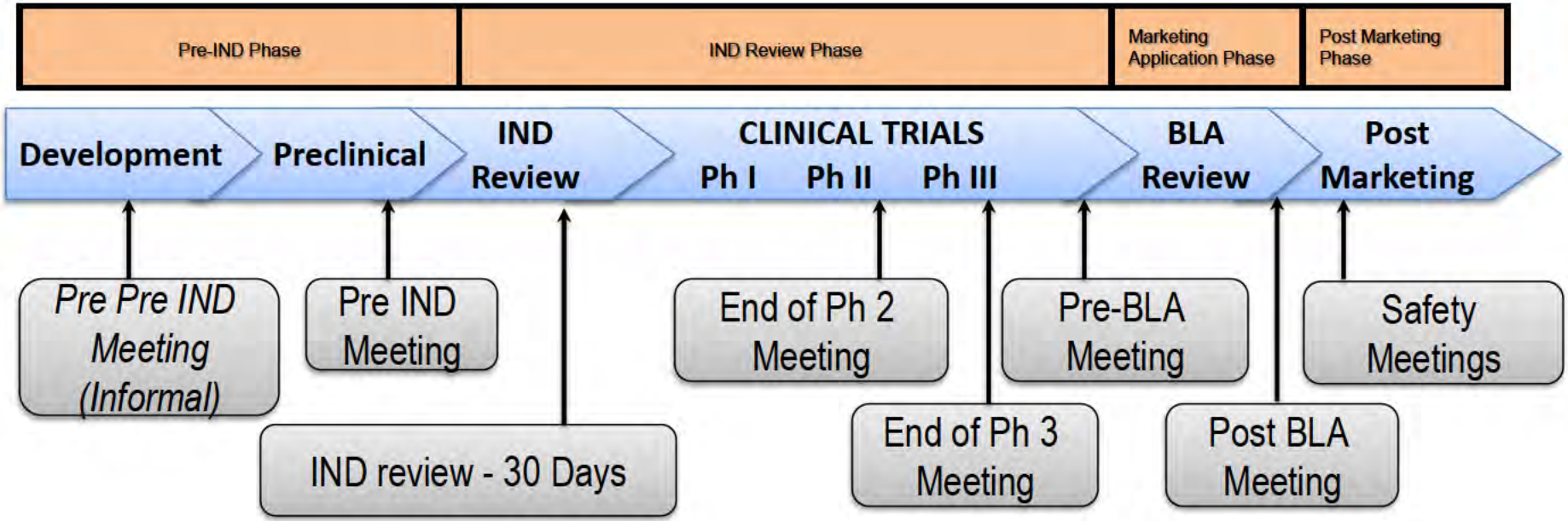
Cautionary Statement Concerning Forward-Looking Statements

This presentation is intended to present a summary of ACT's ("ACT", or "Advanced Cell Technology Inc", or "the Company") salient business characteristics.

The information herein contains "forward-looking statements" as defined under the federal securities laws. Actual results could vary materially. Factors that could cause actual results to vary materially are described in our filings with the Securities and Exchange Commission.

You should pay particular attention to the "risk factors" contained in documents we file from time to time with the Securities and Exchange Commission. The risks identified therein, as well as others not identified by the Company, could cause the Company's actual results to differ materially from those expressed in any forward-looking statements.

Opportunities for Advice



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Safety, Safety, Safety…

Safety is the primary concern

"FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety…"

IND Regulations [21 CFR 312.22 (a) - General Principles of the IND Submission]

Examples of Safety Considerations

- Risks of the delivery procedure
- *Ex vivo* manipulation (e.g., expansion, genetic modification, encapsulation, scaffold seeding)
- Potential inflammatory/immune response to the administered cellular product
- Inappropriate cell proliferation (i.e., tumor formation)
- Inappropriate cell differentiation (i.e., ectopic tissue formation)
- Cell migration to non-target areas/tissues
- Interactions with concomitant therapies

Examples of Preclinical Issues

- Scientific basis for conducting clinical trial
- Data to recommend initial safe dose & dose escalation scheme in humans
- Proof of Concept Studies in relevant animal models
- Toxicology Studies in relevant animal species
  - Identify, characterize, quantify the potential local and systemic toxicities

Preclinical Study Design

- Nonbiased design
  - Randomized assignment to groups
  - Appropriate controls (e.g., sham, vehicle)
  - In-life and postmortem assessments conducted in a blinded manner
- Mimic clinical scenario as closely as possible
  - Use cells intended for clinical use…or analogous cells
  - Cell viability, concentration/formulation, volume, rate of delivery, implant site, number of implants/ injections, etc
  - Delivery system, timing of cell delivery, dosing regimen, etc
  - Anatomical location/extent of the diseased/injured area

Preclinical Study Design (con't)

- Adequate numbers of animals/group to ensure statistically and biologically robust interpretation
- Sufficient study duration and multiple time points - depending on the biology of the product - to allow for adequate assessment of:
  - Functional and morphological outcomes
  - Cell fate
  - Onset and persistence profile of significant findings in target/non-target tissues

Preclinical Study Design (con't)

- Product-dependent endpoints
  - Tumorigenicity
  - Immunogenicity/Inflammation
- Disease-dependent endpoints
  - Visual accuity
- Cell fate following administration
  - Survival/engraftment
  - Integration (anatomical/functional)
  - Transdifferentiation/de-differentiation

Considerations for Species/Model

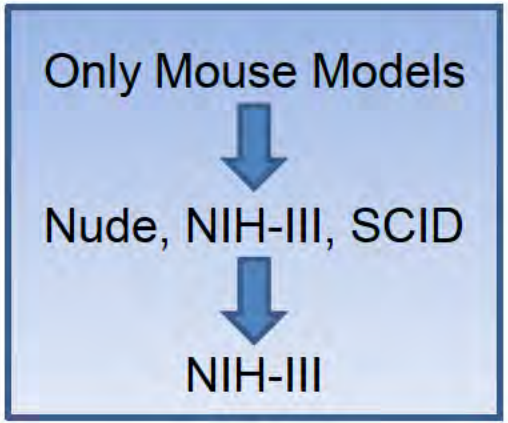
- Appropriate physiological relevance with human
  - Model of disease/injury
  - Local microenvironment may impact the safety of the product
- Route of administration – comparability to clinical
  - Systemic vs. targeted delivery
  - Delivery system/delivery procedure
- Species specificity of the product
- Species specificity of the innate immune response

Considerations for Species/Model (con't)

- Understand the limitations of the species/ model(s) used
- Scientific justification should be provided for the animal species/model(s) used

NIH-III Mice - Practical Choice

- Requirements for Animal Model
  - Minimal Discordant Xenogenic Response
    - Mice have a less aggressive immune response compared to rats and large animals
  - Immunocompromised
  - Pigmented Eye
    - Required for subretinal injection protocol



NIH-III: Only practical choice in view of requirements

- NIH-III (BNX) Mice (NIH-*Lyst* ^{bg}*Foxn1*^{nu}*Btk* ^{xid})
  - Spontaneous mutant T, B & NK cell deficient
  - Used before in cell therapy

Engraft and Function in Animal Models

Functional Rescue observed in Stargardt Mouse Model

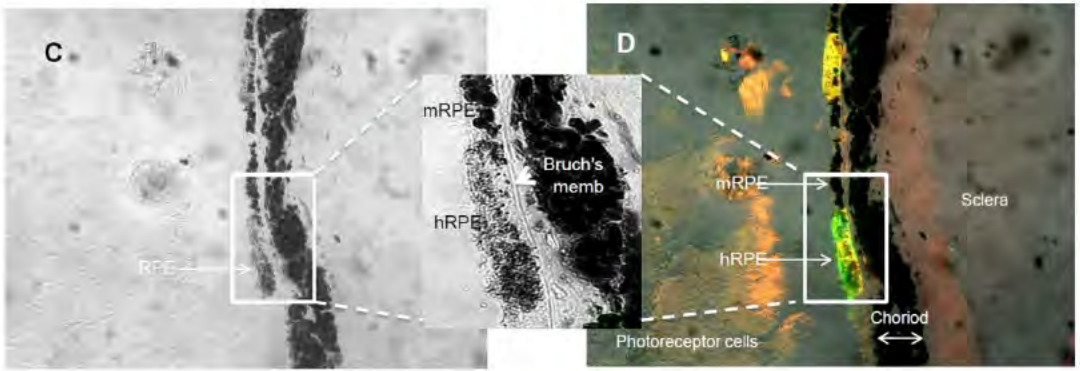
- Efficacious dose established
- Near-normal functional measurements were recorded at >60 days.

Chemically Immunosuppressed RCS Rat Study

- Photoreceptor Rescue
  - Extensive photoreceptor rescue. Photoreceptor layer 5-7 cell layers deep in treated animals versus 1 cell layer deep in untreated control.
- Improved Visual Acuity
  - 100 percent improvement in visual performance over untreated control
  - Restored to 70 percent of normal healthy animals.
- Survival of transplanted cells more than 220 days post-op
- No Tumor Formation
- Normal Pathology
  - No indication of extraneous non-retinal cells in eyes.

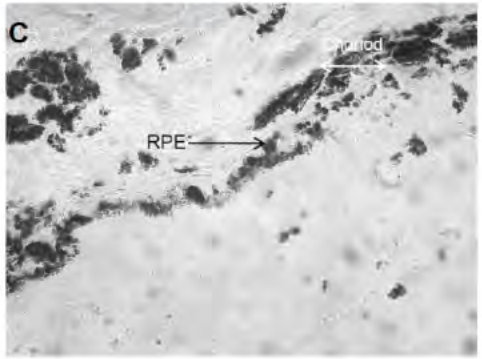
Functional Integration of RPE Cells into RPE layer was Observed

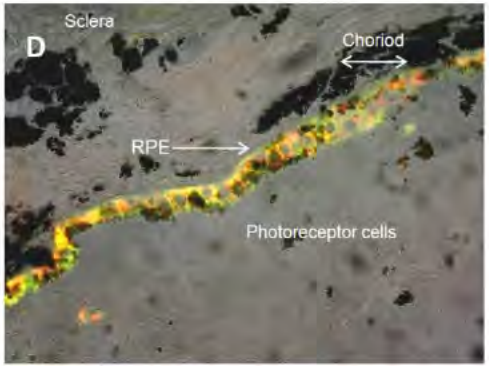
RPE Engraftment – Mouse Model



Human RPE cells engraft and align with mouse RPE cells in mouse eye

For each set: Panel (C) is a bright field image and Panel (D) shows immunofluorescence with anti-human bestrophin (green) and anti-human mitochondria (red) merged and overlayed on the bright field image. Magnification 400x





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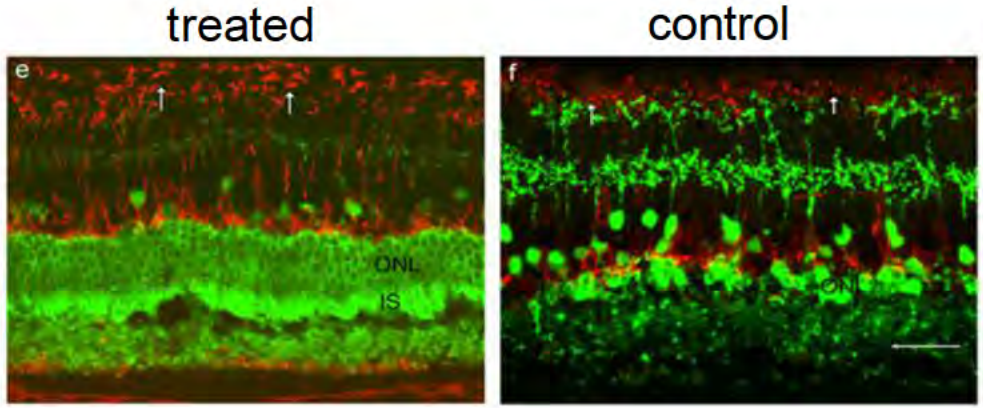
RPE Engraft and Function in Animal Studies

RPE treatment in animal model of retinal dystrophy has slowed the natural progression of the disease by promoting photoreceptor survival.

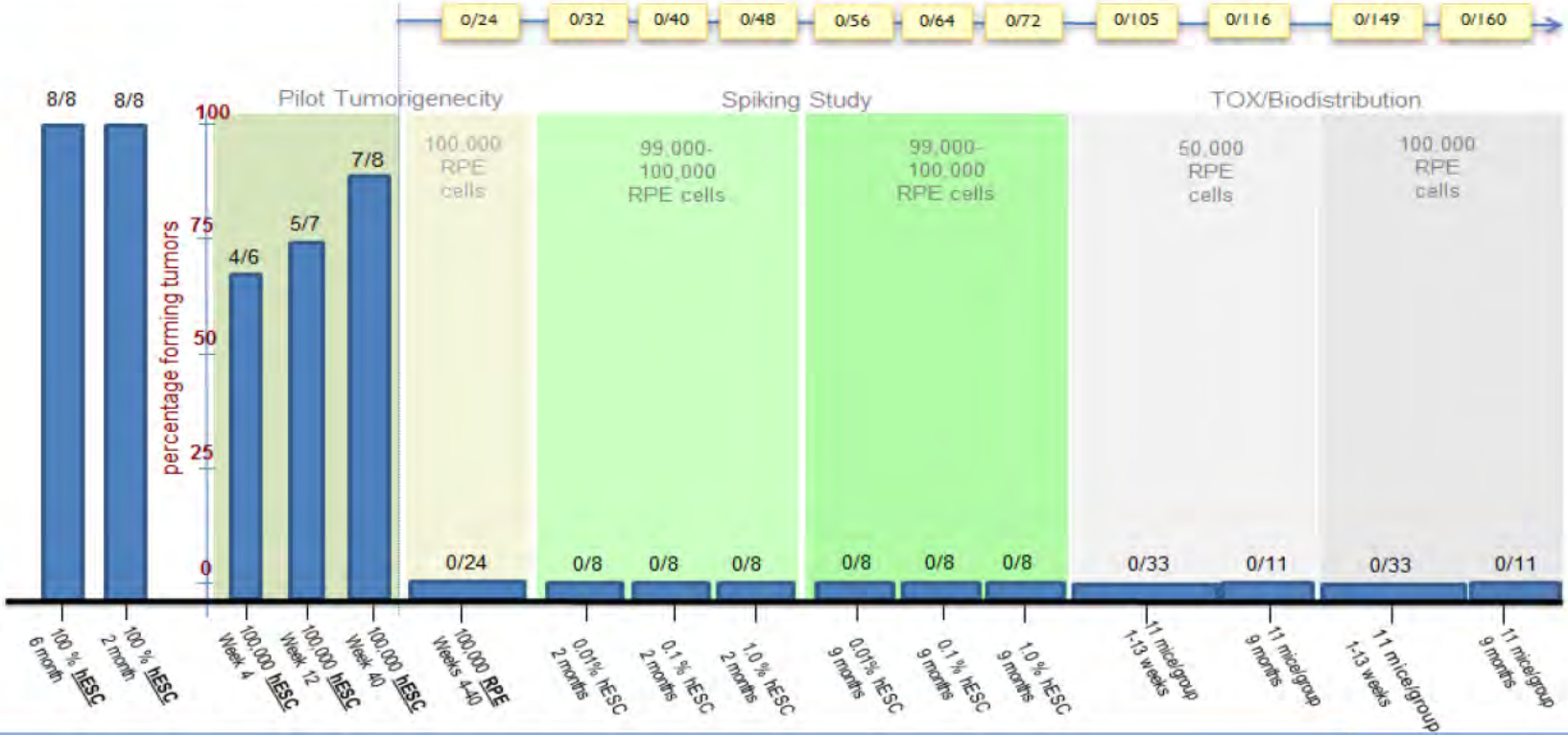


RPE cells rescued photoreceptors and slowed decline in visual acuity

Safety Studies

Extensive Safety Studies Shows Lack of Tumorigenicity

0 of 160
Treated Animals formed tumors



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No Adverse Effects in the Eye

- **No Observed Pathologies**
  - All eye slides were reviewed by a board certified veterinary pathologists.
    - Only typical retinal morphology was observed.
    - No ectopic tissue or abnormal pathology was observed.
    - Histological examination of the retinas demonstrated the presence of human-specific nuclear marker .
    - Staining with human-specific proliferating cell nuclear antigen (PCNA) was negative, indicating that there was no proliferation of the human RPE cells.
  - A safety/biodistribution study was conducted to determine the ability of the cells to migrate or disseminate outside the area of the transplant as well as assess the general safety of the cells in an animal model.

Stem Cell-Based Products

- Fit regulatory definitions of the following:
  - Human cells, tissues, or cellular and tissue based products (HCT/P) (21 CFR 1271.3(d))
  - Biologics (PHS Act)
  - Drugs (FDC Act)
  - Cell therapy
  - Gene therapy- when genetic material is transferred to cells ex vivo

Examples of Safety Concerns

- Defining the intended mode of action
- Characterization of the product, including potency
- Cell differentiation to undesired cell types
- Cell migration/trafficking to nontarget site(s)
- Potential uncontrolled cell proliferation or tumorigenicity
- Immunogenicity
- Graft-vs-host effects
- Interactions with devices, other tissues or drugs in vivo
- For gene-modified cells
  - Potential uncontrolled biological activity of the transgene
  - Alteration of expression of the nontransgenes
  - Insertional mutagenesis

Examples of CMC Issues

- Controls to prevent transmission of infection from the donor or introduction of infectious agents during cell processing

  Donor Testing and screening for relevant communicable diseases
  - Autologous donors recommended but not required
  - Allogeneic donors must comply with 21 CFR 1271 Subpart C
    - HCT/P donor screening is medical history interview, physical assessment and medical record review
    - HCT/P donors are tested using FDA approved or cleared donor screening tests
- Cell banks- adventitious agent testing & characterization
- If mouse feeder layers used- test for the presence of murine viruses (and is a xenotransplantation product)
- Components, reagents, materials qualification

Examples of CMC Issues (con't)

- Account for and control donor to donor variability
- Intrinsic safety concerns, based on cell source or history
- Adequate characterization of the product
  - Identity, purity, potency
  - Additional characterization
- System for product tracking and labeling
  - critical for patient specific products
- Stability of product and or cell line
  - number of passages/ doublings over time
  - maintain desired differentiation properties
  - karyotypic alterations
- Product comparability for manufacturing changes

GMP Manufacturing

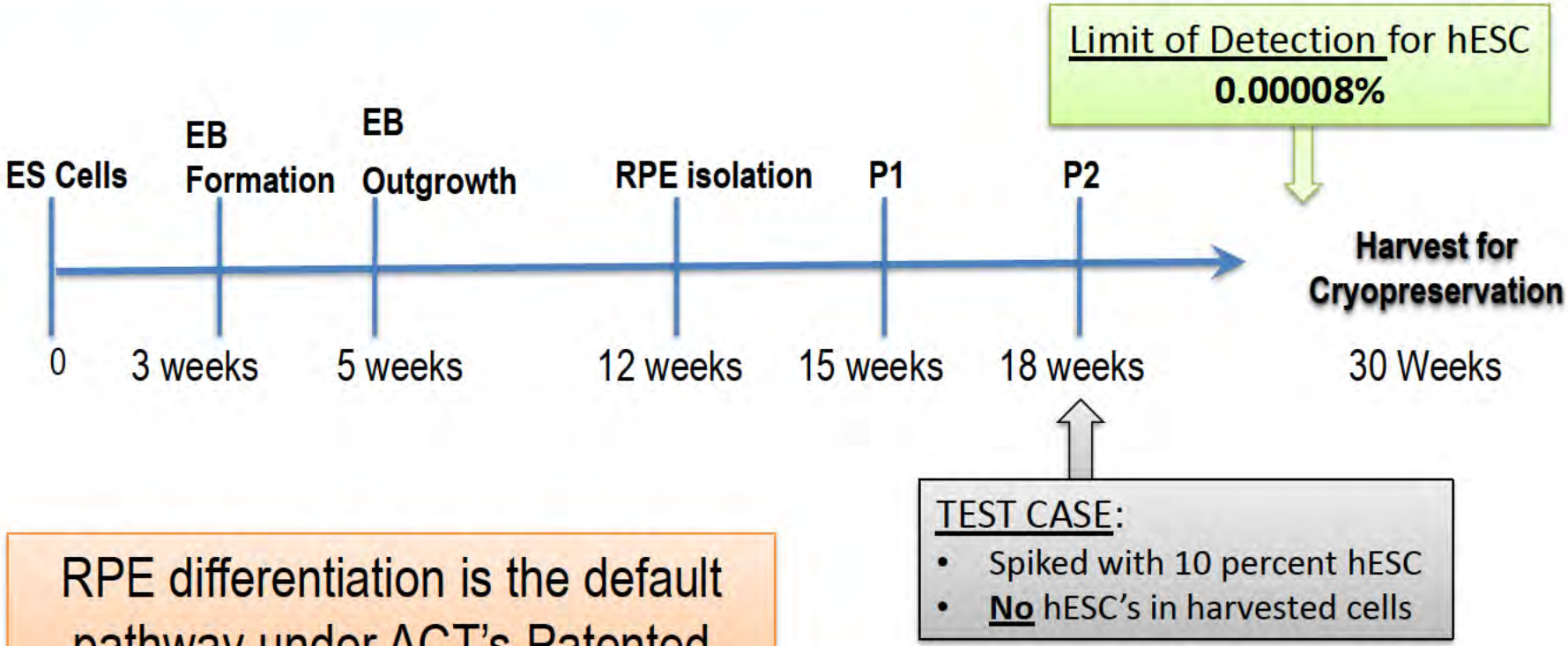
- RPE cells are derived from an extensively tested hES MCB.
- Entire process is aspetic; no antibiotics used (~110 days).
- Use of MEF feeders classifies RPE as a xeno-therapeutic product.
- Cryopreserved bulk product is extensively tested prior to release.
- Bulk product is thawed and formulated for therapeutic on the day of use.

- Some unique quality tests include:
  - Screening for the absence of hES cells (IFA)
  - Assessing the extent of differentiation by:
    - gene expression (q-RT-PCR)
    - protein deposition (IFA staining)
    - morphological evaluation
    - extent of pigmentation (melanin)
    - potency by phagocytosis assays (FACS)

In-Process Quality Testing

- Frequent Morphological Assessments (1-2days)
- Periodic Sterility Testing (~ every 30 days)
- Karyotyping at Embryoid Body Formation
- Absence of hES Cells at Seeding of Passage 2 RPE Cells
- Immunohistochemical Staining for RPE Markers (Passage 1 and 2)

Differentiation Media is Not Permissive for hESCs



RPE differentiation is the default pathway under ACT's Patented Culture Conditions

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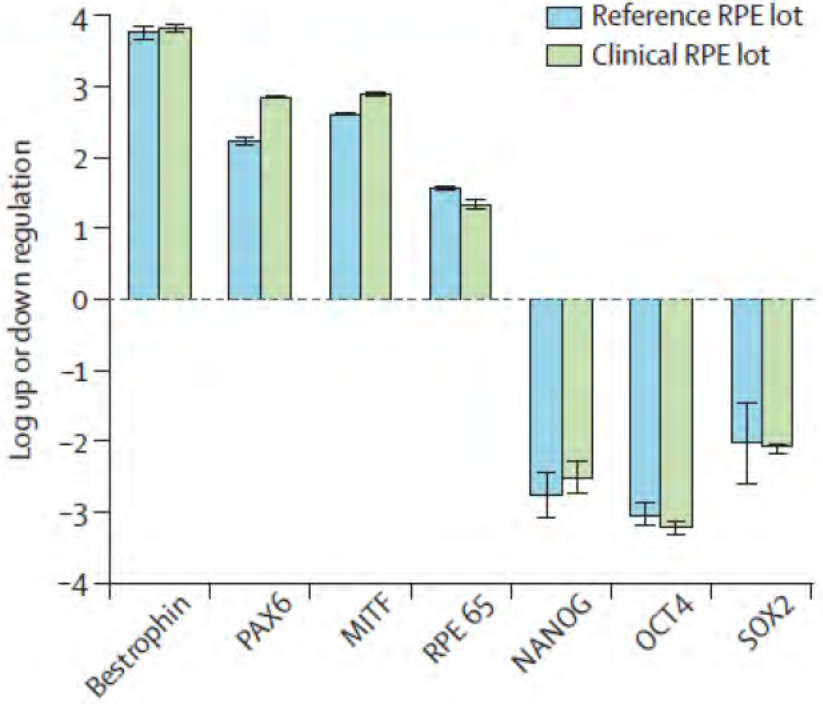
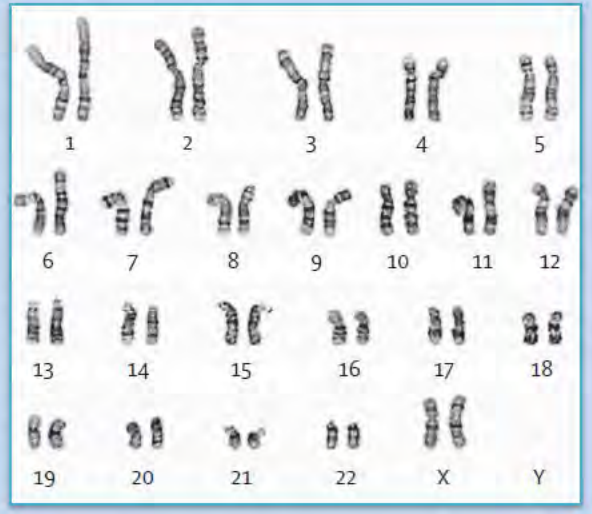
Characterizing Clinical RPE Lots

Up-regulation of RPE markers and down-regulation of hESC markers





Normal female (46 XX) karyotype of the clinical RPE lot.

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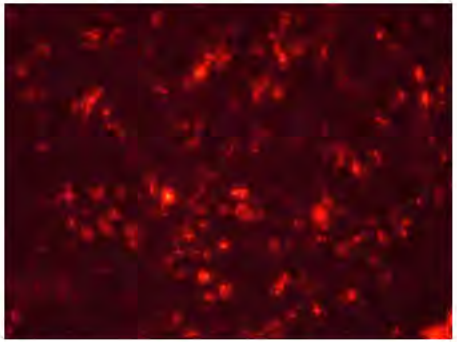
Characterizing Clinical RPE Lots

Quantitative Potency Assay

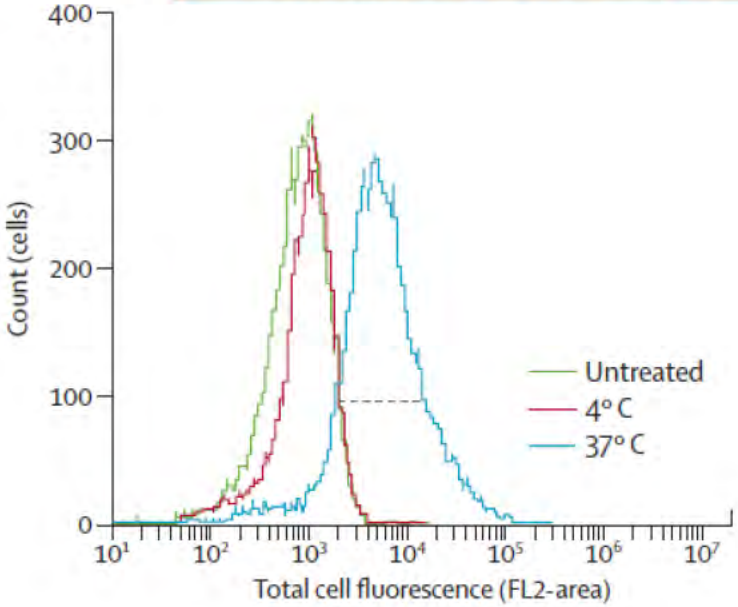
RPE cell potency of each lot is assessed by phagocytosis (critical function *in vivo)* of fluorogenic bioparticles.

4 C



37 C

Flow cytometry histogram showing phagocytosis of pHrodo bioparticles



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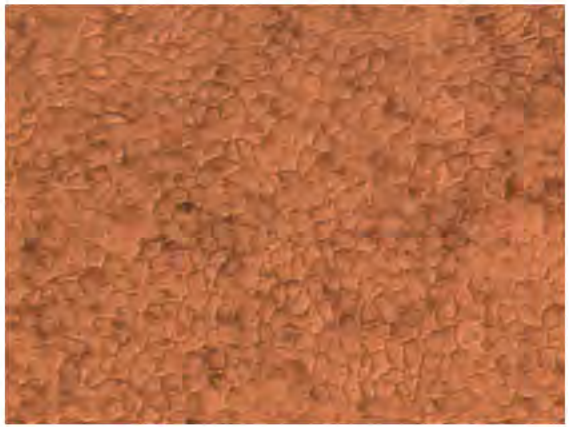
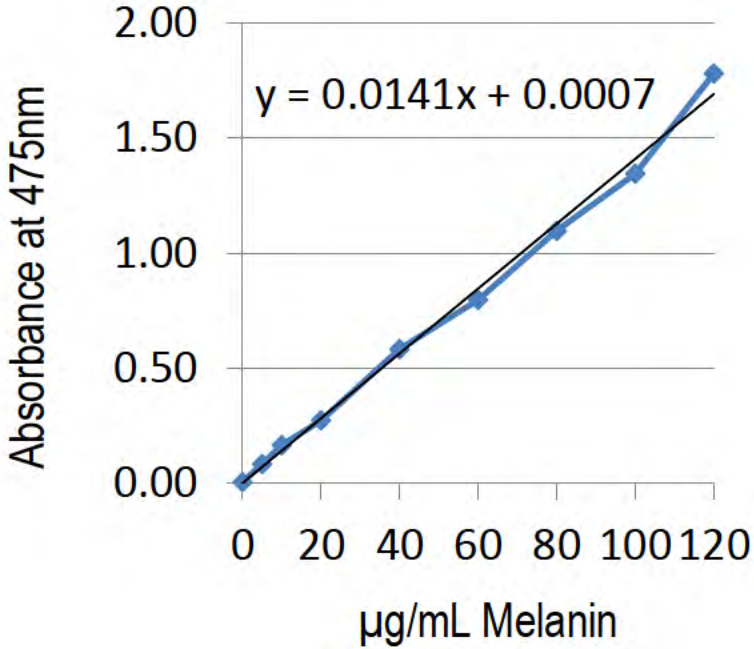
Effects of Pigmentation

Melanin content can be measured spectrophotometrically and used to determine the optimal time to harvest and cryopreserve RPE.





Administration of Stem Cell Products

- Delivery of stem cells to certain anatomic locations may require novel procedures and/or novel delivery devices
- Compatibility of cells with the device
- Preclinical testing of cells and device
- Delivery procedure used during clinical trial and beyond
  - Training of clinical investigators

SMD Trial- FDA Hold Issues

FDA identified Clinical Hold Issues following the review of ACT's IND#14220 for Stargardt's Macular Dystrophy. The major issues concerned product testing, addressing PHS Xenotransplantation Guidelines and the adequacy of preclinical safety data.

- **Manufacturing**
  - **Testing**
    - All required testing recommended by FDA was performed
    - Lot release criteria to be adjusted based on additional testing
  - **Xenotransplantation Issues**
    - ACT modified manufacturing of clinical product following additional FDA recommendations.
  - **Purity**
    - FDA's initial response was to question why PCR was not the primary release assay for detecting contamination with hES cells.

Addressing Xeno Guidelines

- Previous mouse fibroblast feeder cells (MEFs) were derived from time sensitive pregnancies from a closed colony
- ACT established new MEFS to address All FDA recommendations.
- ACT now generates clinical product following all additional FDA recommendations.

Addressing Preclinical Issues

- Justification of animal model
  - Primary goal was to select an animal model that was optimal for hRPE cell survival
- Robustness of preclinical data
  - Additional assessments based upon FDA recommendations
- Histological Assessment
  - Additional assessments based upon FDA recommendations

Addressing Clinical Issues

- The Informed Consent document will include language informing patients they will be receiving a xenotransplantation product.
- The investigational plan will address the actions to be taken in the event that the 14 day sterility test is determined to be positive after the product is administered.
    - Any sterility failure, results of investigation of the cause and any corrective actions, will be submitted in an information amendment.
- The clinical investigator will evaluate the subject for any signs of infection that may be attributable to the product sterility failure.
    - Any serious and unexpected adverse drug experience that could be from administration of the sterility failure of the cellular product will be reported to the FDA and IRBs.

Retinal Pigment Epithelial Cells - Rationale

The RPE layer is critical to the function and health of photoreceptors and the retina as a whole.

- RPE cells secrete trophic factors and impact on the chemical environment of the subretinal space.
  - » recycle photopigments
  - » deliver, metabolize and store vitamin A
  - » transport iron and small molecules between retina and choroid
  - » maintain Bruch's membrane
- RPE loss may lead to photoreceptor loss and eventually blindness, such as dry-AMD
- Loss of RPE layer and Bruch's membrane is substantial feature underlying development of dry-AMD, and may be involved in progression from dry-AMD to wet-AMD

RPE Clinical Program – to date

- Dry AMD
  - IND **cleared** in December 2010

ClinicalTrials.gov
US: NCT01345006, NCT01344993
UK: NCTO1469832

- Stargardt's (SMD) Disease
  - IND **cleared** in November 2010
  - European CTA **cleared** 2011
  - Orphan Drug Designation granted in U.S. and Europe

JULES STEIN EYE INSTITUTE

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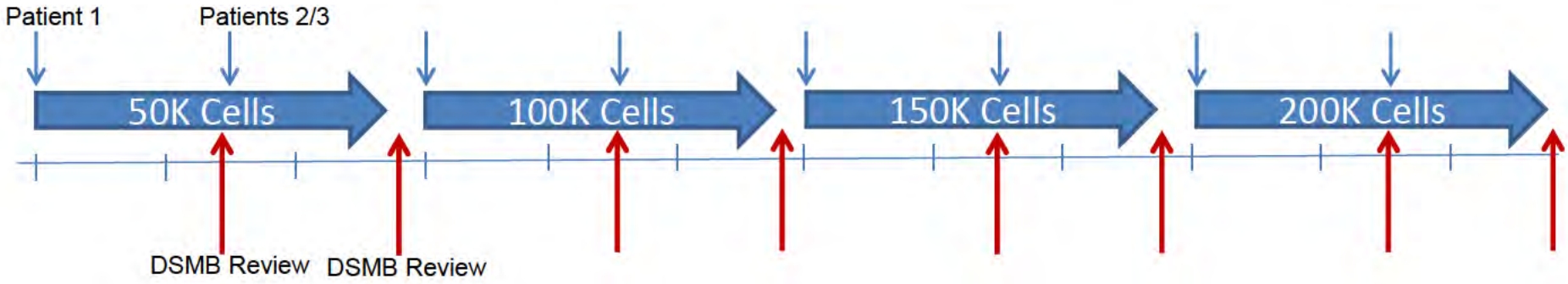
Examples of Clinical Issues

- Administration procedure
  - Standard medical practice? Special instrument or kit?
- Optimal dose and administration
  - Starting dose level/dose escalation scheme
  - Route of administration
  - Dose schedule
- Define appropriate patient population
- If immunosuppression will be used:
  - Is the dose-schedule justified?
  - Long-term vs short term
  - Single drug vs a combination regimen
- Safety Monitoring plans
- Safety Reporting requirements

Phase I - Clinical Trial Design

SMD and dry AMD Trials approved in U.S., SMD Trial approved in U.K.

- Safety and Tolerability Studies
  - 12 Patients for each trial, ascending dosages of 50K, 100K, 150K and 200K cells.
  - Patients are monitored –for safety, including extensive examinations of retina
  - DSMB Review
    - For each cohort, 1st patient treatment followed by 6 week DMSB review before remainder of cohort.
    - DSMD review of 4 week patient data for remaining patients prior to treating next higher dose cohort



Phase I – SMD endpoints

PRIMARY ENDPOINTS: ASSESSMENT OF SAFETY	The transplantation of hESC-derived RPE cells MA09-hRPE will be considered safe and tolerated in the absence of: • Any grade 2 (NCI grading system) or greater adverse event related to the cell product • Any evidence that the cells are contaminated with an infectious agent • Any evidence that the cells show tumorigenic potential
SECONDARY ENDPOINTS	**Evidence of successful engraftment will consist of:** • Structural evidence (OCT, fluorescein angiography, autofluorescense photography, slit-lamp examination with fundus photography) that cells have been implanted in the correct location • Electroretinographic evidence (mfERG) showing enhanced activity in the implant location **Evidence of rejection will consist of**: • Structural (imaging) evidence that implanted MA09-hRPE cells are no longer in the correct location or the presence of vascular leakage. • If enhanced electroretinographic activity is observed after the transplantation, subsequent electroretinographic evidence that activity has returned to pre-transplant conditions may be an indication of graft rejection

Phase I – Dry AMD endpoints

PRIMARY ENDPOINTS: ASSESSMENT OF SAFETY	The transplantation of hESC-derived RPE cells MA09-hRPE will be considered safe and tolerated in the absence of: • Any grade 2 (NCI grading system) or greater adverse event related to the cell product • Any evidence that the cells are contaminated with an infectious agent • Any evidence that the cells show tumorigenic potential
SECONDARY ENDPOINTS **Additional secondary endpoints will be evaluated as exploratory evaluations for potential efficacy endpoints.**	**Evidence of successful engraftment will consist of:** • Structural evidence (OCT, fluorescein angiography, autofluorescense photography, slit-lamp examination with fundus photography) that cells have been implanted in the correct location • Electroretinographic evidence (mfERG) showing enhanced activity in the implant location **Evidence of rejection will consist of**: • Structural (imaging) evidence that implanted MA09-hRPE cells are no longer in the correct location or the presence of vascular leakage. • If enhanced electroretinographic activity is observed after the transplantation, subsequent electroretinographic evidence that activity has returned to pre-transplant conditions may be an indication of graft rejection

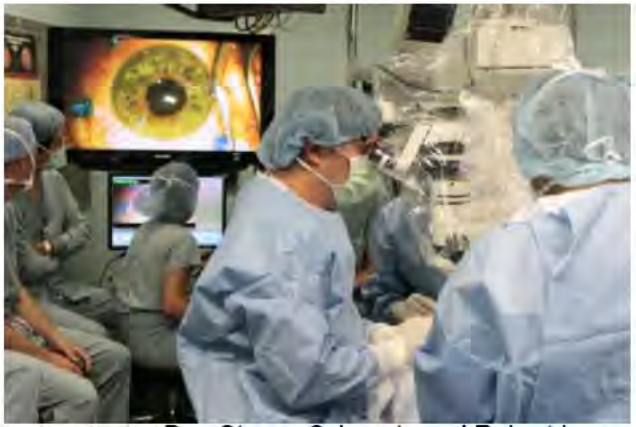
RPE Clinical Program – to date

- **US Clinical Trial Sites**
  - Jules Stein Eye (UCLA)
  - Wills Eye Institute
  - Bascom Palmer Eye Institute
  - Massachusetts Eye and Ear Infirmary
  - Status
    - Stargardts: 1st cohort completed
    - DSMB clearance granted to begin treating next cohort
    - Screening for 4th patient (first patient at escalated dose)
    - Dry AMD: 1st cohort completed;
      will submit data on patients 2 & 3 to DSMB in late May
- **European Clinical Trial Sites**
  - Moorfields Eye Hospital
  - Aberdeen Royal Infirmary
  - Status
    - 1st SMD (Europe) patient treated (20 January 2012), **about to treat patients 2 & 3**

Dr. James Bainbridge, Moorfields Eye Hospital

Surgical Overview

- Vitrectomy including surgical induction of posterior vitreous separation from the optic nerve was carried out
  - 25 Gauge Pars Plana Vitrectomy
  - Posterior Vitreous Separation (PVD Induction)
  - Subretinal injection of hESC-derived RPE cells in a volume of 150µl is delivered into a pre-selected area of the pericentral macula
  - Bleb Confirmation
  - Air Fluid Exchange



Drs. Steven Schwartz and Robert Lanza

Straight forward surgical approach;
Can be performed on outpatient basis

Preliminary Results

- Dry AMD
  - *The dry AMD patient is a 77 year old female with baseline BCVA of 20/500, that corresponded to 21 letters in the ETDRS chart.*

- Stargardt's (SMD) Disease
  - *The SMD patient is a 51 year old female with baseline best corrected visual acuity of hand motion that corresponded to 0 letters in the ETDRS chart.*

July 12, 2011: First Patients in each trial were treated by Dr. Steven Schwartz, M.D at Jules Stein Eye Institute (UCLA)

Preliminary Results

- After surgery, structural evidence confirmed cells had attached and continued to persist during study.
- No signs of hyperproliferation, abnormal growth, or immune mediated transplant rejection in either patient.
- Anatomical evidence of hESC-RPE **survival and engraftment**.
- Clinically **increased pigmentation** at the level of the RPE within the bed of the transplant beginning at postoperative week 1.


THE LANCET

Embryonic stem cell trials for macular degeneration: a preliminary report

Steven D Schwartz, Jean-Pierre Hubschman, Gad Heilwell, Valentina Franco-Cardenas, Carolyn K Pan, Rosaleen M Ostrick, Edmund Mickunas, Roger Gay, Irina Klimanskaya, Robert Lanza

23 January 2012
Published results for first SMD and Dry AMD Patients – 4 month time point

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Preliminary Results

Recorded **functional visual improvements** in both patients.

- SMD Patient: Best corrected visual acuity improved from hand motions to 20/800 and improved from 0 to 5 letters on the ETDRS visual acuity chart in the study eye.
- Dry AMD Patient: Vision improved in the patient with dry age-related macular degeneration (21 ETDRS letters to 28).

SMD Patient

	BCVA	ETDRS (number of letters)
Fellow eye		
Baseline	Hand motion	0
1 week	Hand motion	0
2 weeks	Hand motion	0
3 weeks	Hand motion	0
4 weeks	Hand motion	0
6 weeks	Hand motion	0
8 weeks	Hand motion	0
12 weeks	Hand motion	0
Operated eye		
Baseline	Hand motion	0
1 week	Counting fingers	0
2 weeks	Counting fingers	1
3 weeks	Counting fingers	3
4 weeks	20/800	5
6 weeks	20/800	5
8 weeks	20/800	5
12 weeks	20/800	5

Ongoing Results

Six Month Follow-up:

- Visual acuity gains remain stable for both patients; SMD Patient has slight improvement.
- Similar trends observed for latest patients

Thank you

For more information, visit www.advancedcell.com

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