

Leading Regenerative Medicine

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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.



Manufacturing Platform – Pluripotent Stem Cell Sources



Multiple Pluripotent Cell Platforms

Single Blastomere-derived Embryonic Stem Cells

- Generating hESC <u>without</u> Destruction of Embryo
- Utilizes a single cell biopsy
- Our hESC lines exhibit all the standard characteristics and the ability to differentiate into the cells of all three germ layers both in vitro and in vivo.

Induced Pluripotency Stem Cells (iPS)

- Early Innovator in Pluripotency (before iPS was even a term!)
- Recipient of National Institutes of Health Director's Opportunity Award
- Seminal paper identifying replicative senescence issue for vector-derived iPS cells
- Leading publication on protein induced iPS lines avoids genetic manipulation with nucleic acid vectors
- Controlling Filings (earliest priority date) to use of OCT4 for inducing pluripotency



<u>Final Product Definition</u>: hESC-derived products will be manufactured using a cell line made in 2005 from single cell isolated without the destruction of any embryos



Therapeutic Pipeline -Ocular Programs





Management of Ocular Surfaces

Protection of Retinal Ganglion cells (Glaucoma)





RPE Clinical Program



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 provide trophic support and detoxification activities to photoreceptor space.
 - » Recycle photopigments
 - » Deliver, metabolize and store vitamin A
 - » Phagocytize and clear cellular waste
 - » Maintain Bruch's membrane

No other cell type can perform this complete set of functions

- » Absorbs incident light, protects space from UV damage
- RPE loss leads to photoreceptor loss and eventually blindness, such as dry-AMD
- Loss of RPE layer and appears to lead to decline of Bruch's membrane, leading progression from dry-AMD to wet-AMD
- Discrete differentiated cell population as target
- Failure of target cells results in disease progression



RPE Cells Therapy



On the Rise: Population demographics ("baby boomers") combined with increased longevity predicts an increase of 50 percent or more in the incidence rate of AMD.

ACT's RPE Cell Therapy should effectively address the full range of dry AMD patients.

- Halt the progression of disease and vision loss in early stage patients
- Restore some visual acuity in later stage patients

Dry AMD represents more than 90 percent of all cases of AMD

North America and Europe alone have more than 30 Million dry AMD patients who should be eligible for our RPE cell therapy



RPE Engraftment and Function – Pre-clinical



Injected human RPE cells recapitulates correct monolayer structure in eye

> **RPE cells rescued photoreceptors** and slowed decline in acuity in animal models





GMP Manufacturing

- Established GMP process for differentiation and purification of RPE
 - Virtually unlimited supply
 - Pathogen-free GMP conditions
 - Minimal batch-to-batch variation
 - Characterized to optimize performance
 - Virtually identical expression of RPE-specific genes to controls

Ideal Cell Therapy Product

- Centralized Manufacturing
- Small Doses
- Easily Frozen and Shipped
- Simple Handling by Doctor





Surgical Overview



Procedure:

- 25 Gauge Pars Plana Vitrectomy
- Posterior Vitreous Separation (PVD Induction)
- Subretinal hESC-derived
 RPE cells injection
- Bleb Confirmation
- Air Fluid Exchange



Preliminary Results

- Structural evidence confirmed cells had attached and persisted
- No signs of hyperproliferation, abnormal growth, or rejection
- Anatomical evidence of hESC-RPE
 survival and engraftment.
- Clinically **increased pigmentation** within the bed of the transplant
- Recorded functional visual improvements in both patients

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



Images of hESC-RPE transplantation site in SMD Patient



SD-OCT images

Demonstrate survival and engraftment of RPE The injected RPE cells migrate to the desired anatomical location



Intellectual Property – RPE Program

Dominant Patent Position for Treating Retinal Degeneration

• <u>US Patent 7,794,704</u> broadly cover methods for treating retinal degeneration using human RPE cells differentiated from human embryonic stem cells (hESCs).

Broad Coverage for Manufacturing RPE Cells from hESC

• U.S. Patents 7,736,896 and 7,795,025 are broadly directed to the production of retinal pigment epithelial (RPE) cells from human embryonic stem cells.

Patent Filings include claims covering Cell Cure Neurosciences, Pfizer/Coffey and Retinal Patch Technologies.

Coverage for RPE Cells derived from other pluripotent stem cells (including iPSC)

- Earliest priority date relates back to 2004 filings
- Methods of manufacturing, use of RPE cells, and pharmaceutical formulations
 - Includes adherent monolayers for transplantation
 - Includes iPS (any pluripotent stem cell that expresses Oct-4, alkaline phosphatase, SSEA-3 and SSEA-4)

Vigilant Filing on Improvements

- Extends patent life cycle, with significance to commercialization
- Include composition-of-matter claims (cell preparations, pharmaceutical preparations, etc.)
- Examples: degree of pigmentation, cell denisty or preparation, phagocytic activity
 - Distinguished from adult RPE cell preparations telomere length, A2E and lipofuscin content of cells, lack of accumulated UV damage



Price Justification

	Justification
More Important	Clinical Unmet Need
	Clinical Efficacy
	Patient Prevalence
1 655	Pharmaco- economic Data
Important	Patient Advocacy Groups

Both private and public payers are most interested in understanding how new therapies will deliver enhanced clinical value.

RPE Therapy provides pricing justification across all categories of consideration





ACT MSC Program



Mesenchymal Stem Cells in Therapy

Mesenchymal stem cells (MSCs) regulate immune responses, providing therapeutic potential for treating autoimmune or inflammatory diseases.

- MSCs can be used allogeneic: <u>without matching</u> between donors and recipients.
- Adult-derived MSCs have already been used therapeutically in clinical trials.
- Potential uses in a wide range of autoimmune conditions, such as multiple sclerosis, lupus, and Crohn's disease, among others.

An "off-the-shelf" cellular drug ready for treatment of a wide range of inflammatory and autoimmune diseases.



Adult Mesenchymal Stem Cells

<u>BUT</u>: Replicative capacity is a big limitation for adult sources of allogeneic MSC therapies.

- Impacts on Cell Banking
 - Limitation on the number of doses that can be generated from adult donors
 - A few hundred to a thousand doses per cell bank per donor.
 - Requires constantly creating and validating MSC banks from new donors
- Impacts on Potency
 - Passaging reduces immunomodulatory/immunosuppressant potency of MSC's.
- <u>Causes Genomic instability</u>:
 - Genomic stability is an important concern for clinical use of MSC
 - Lack of replicative capacity of adult-derived MSC's creates risk of genomic instability.



hESC/iPS – derived MSC

ACT Proprietary Process

- hESC- and iPS-derived MSCs can be expanded to large numbers in vitro
 - Long telomeres so can divide many more times than adult cells
 - Avoids replicative capacity problem of "old" adult MSC's
 - Creates a <u>renewable</u> cell source as Master Cell Bank

Advantages over Adult MSC

- Less labor-intensive
- Single Bank simplifies FDA/regulatory process
 - No need to regularly derive new banks
 - Quality controls are easier to manage
- Larger yield of MSCs 33,000 fold greater yield relative to adult MSC

Proprietary scalable manufacturing for generating "young" MSCs



Preliminary Data

Animal Models

- hESC-derived MSCs substantially <u>decrease and reverse</u> disease conditions in autoimmune models.
- hESC-derived MSCs are far more potent than adult (BM) derived MSCs.

Potential implications of increased potency ...

- utility of hESC- and iPS-derived MSCs in a greater range of diseases.
- reduced number of cells per dose improved safety profile.

Higher immunosuppressive potency relative to adult MSC





Thank you For more information, visit www.advancedcell.com

